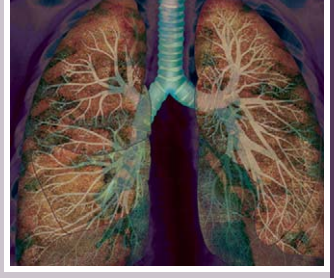
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

SECTION XIII

PULMONARY MANIFESTATIONS OF SYSTEMIC CONDITIONS



58 Pulmonary Complications of Hematopoietic Stem Cell Transplantation

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Introduction

Hematopoietic stem cell transplantation (HSCT) refers to the transplantation of stem cells from various sources (bone marrow, growth factor–stimulated peripheral blood, and umbilical cord blood) for the treatment of malignant and nonmalignant hematologic, autoimmune, and genetic diseases.

Despite advances in HSCT, transplant recipients remain at high risk for serious and fatal complications developing as a consequence of cytoreductive conditioning regimens used before transplant, immunologic sequelae following engraftment of allogeneic lymphoid cells (which mediate graft-versus-host responses), the patient's immunosuppressed state, and infections secondary to immunosuppression. Pulmonary complications after HSCT are common and contribute considerably to the morbidity and mortality of transplant recipients, and respiratory failure is the most common cause of critical illness after HSCT.

Types of HSCT

There are three types of stem cell transplantation: autologous, syngeneic, and allogeneic. In autologous transplants, the stem cells serving as a marrow graft are derived from the patient themselves; in syngeneic transplants, the stem cells are derived from a genetically identical twin; and in allogeneic transplants, the stem cells are taken from a nonidentical sibling or unrelated donor. Because autologous and syngeneic transplants involve stem cells that are immunologically identical to the recipient, reactions between graft and host are avoided. In allogeneic transplants, mismatch between donor and recipient human leukocyte antigens (HLAs) mediate graft-versus-host disease (GVHD) and graft rejection. The decision about which type of transplant to perform is based on the nature and stage of the underlying disease, on whether a suitable donor is available, and the medical condition of the recipient. The advantages to allogeneic transplantation over autologous transplantation include a higher likelihood that the stem cell product is free of tumor contamination and the presence of graft-versus-tumor activity.

Indications for HSCT

The main indication for HSCT is the treatment of hematologic malignancies and solid tumors, but it is also used in many nonmalignant disorders.

Nonmalignant Conditions Treated with HSCT

1. Autoimmune diseases (rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, multiple sclerosis)
2. Amyloidosis
3. Aplastic anemia
4. Hemoglobinopathies (thalassemia and sickle cell anemia)
5. Other genetic disorders and inborn errors of metabolism (severe combined immunodeficiency, Wiskott–Aldrich syndrome)

Conditioning Regimens in HSCT

One prerequisite for successful HSCT is conditioning therapy before transplant, which serves to ablate the bone marrow, eradicate tumor cells, and induce immunosuppression to permit engraftment and prevent rejection of the transplanted donor stem cells. These preparative regimens consist of high-dose chemotherapy with or without total body irradiation (TBI) and contribute considerably to the pulmonary complications seen after transplantation. Irradiation is generally omitted from autologous conditioning regimens because of concerns for late toxicity and secondary malignancies.

Most myeloablative regimens used before allogeneic transplantation consist of cyclophosphamide administered either with busulfan or TBI. Prophylaxis after allogeneic transplant to prevent GVHD usually involves methotrexate, cyclosporine, corticosteroids, or *in vitro* T-cell depletion of the graft before infusion.

"Minitransplantation," "nonmyeloablative," or "reduced intensity" conditioning regimens were developed in the late 1990s to reduce the toxicity profile associated with myeloablative regimens and are used primarily in older patients and those with multiple comorbidities who may not tolerate the more intense conditioning regimens. These less intense preparative regimens usually involve purine analogs like fludarabine in conjunction with immunosuppressive chemotherapeutic agents, low-dose TBI, total lymphoid irradiation, antithymocyte globulin, or other antibody preparations. In contrast to traditional myeloablative preparations, these regimens do not ablate host hematopoiesis but only immunosuppress sufficiently to allow engraftment of the donor stem cells and rely on the graft to eradicate cancer by means of the graft-versus-malignancy effect. These reduced-intensity conditioning regimens are associated

with reduced transplant-associated morbidity and lower incidence of pulmonary complications after transplantation.

Pulmonary Complications of Hematopoietic Stem Cell Transplantation

Pulmonary complications after HSCT are common, with an incidence of 40–60% and with up to one third of recipients requiring intensive care after transplantation. Respiratory failure is the most common cause of critical illness, and pneumonia is the leading infectious cause of death after HSCT.

Pulmonary complications can occur early or late in the posttransplant course, can be due to infectious and noninfectious etiologies, and can present with assorted radiographic findings. The pulmonary complications of HSCT also vary depending on the indication for, type of, and preparative regimen preceding stem cell transplantation.

Key differences between pulmonary complications after autologous HSCT compared with allogeneic HSCT result from the fact that cellular interactions between graft and host cells are essentially eliminated with autologous transplantation, obviating the need for immunosuppression to prevent or treat GVHD. As such, autologous transplantation is associated with lower incidence of infection (particularly with viral pneumonias/CMV pneumonitis, invasive fungal disease, and other opportunistic infections such as *Toxoplasmosis*) and late airflow obstructive defects.

Risk Factors for Development of Pulmonary Disease After HSCT

(Box 58-1)

Relapse status at time of transplant and donor–recipient HLA mismatching/nonidentity are risk factors for pulmonary complications and mortality after HSCT. Active phase of malignancy, age greater than 21 years, and receipt of HLA-nonidentical donor marrow are risk factors for respiratory failure after HSCT.

Abnormalities in pretransplant pulmonary function testing may be predictive of subsequent risk of pulmonary complications and mortality. Reduced diffusing capacity and increased alveolar-arterial oxygen gradient are independent risk factors for interstitial pneumonitis and are also independently associated with increased early mortality after HSCT.

Measurement of cytokine levels in plasma and BAL fluid before transplant may also help predict patients at risk for posttransplant pulmonary complications. Patients with elevated levels of transforming growth factor (TGF)-β in plasma, TGF-α in BAL fluid, and granulocyte-macrophage colony-stimulating factor (GM-CSF) in BAL fluid seem to be at increased risk for pulmonary complications. One study showed that elevated pretransplant TGF-β levels in patients with breast cancer undergoing autologous HSCT were associated with increased posttransplant risk of pulmonary toxicity and hepatic venoocclusive disease.

Recipients of allogeneic transplantation, all of whom require administration of immunosuppressive agents after transplant to treat and prevent GVHD, have more infectious complications than recipients of autografts. This is not only due to chronic immunosuppression, but also because GVHD itself causes an immunodeficient state by affecting mucosal surfaces, the reticuloendothelial system, and bone marrow. These factors predispose allogeneic recipients to fatal viral pneumonias, multidrug-resistant bacteria, and invasive fungi. Similarly, bronchiolitis obliterans is almost exclusively seen after allogeneic HSCT.

BOX 58-1 Risk Factors for Pulmonary Disease After HSCT

- Donor-recipient HLA mismatch
- Relapse status
- Active phase of malignancy
- Age >21 y
- Pretransplant pulmonary function abnormalities
  - Reduced diffusing capacity
  - Increased alveolar-arterial oxygen gradient
  - Restrictive lung disease
  - FEV_1 ≤80% predicted
- Elevated pretransplant cytokine levels (TGF-β, TGF-α, GM-CSF)
- Allogeneic transplantation
  - GVHD and type of GVHD prophylaxis
- Renal disease

Time Course

Specific pulmonary complications associated with HSCT tend to occur in a relatively well-defined time line. The timing and intensity of cytoreductive therapies and the pattern of immune reconstitution that follows influence the duration of these intervals.

Preengraftment

The preengraftment phase (i.e., 0–30 days after transplant) is characterized by prolonged neutropenia and breaks in the mucocutaneous barrier. Accordingly, infectious complications are expected and primarily caused by bacterial and fungal infections. However, surgical lung biopsy in patients receiving HSCT with radiographic infiltrates who are receiving broad-spectrum antibiotics have shown that during this time, the prevalence of infection is low at 19% and that pulmonary complications are primarily noninfectious related to regimen-related toxicities (Box 58-2).

Early Postengraftment

The early postengraftment period spans days 30–100 after transplant and is characterized by persistent impairment in cellular and humoral immunity, in part determined by exogenous immunosuppression, GVHD, deficiency of immunoglobulins, and a loss of protective alveolar macrophages. During this period, neutropenia has usually resolved, decreasing the risk of bacterial and fungal infections. The epidemiology of infectious etiologies thus changes to involve predominantly viral infections, especially cytomegalovirus (CMV). With the routine use of antivirals for CMV prophylaxis, however, the incidence of posttransplant CMV pneumonia has decreased substantially. Noninfectious etiologies during this time include engraftment syndrome and delayed pulmonary toxicity syndrome.

Late Postengraftment

The late postengraftment period begins at day 100 after transplant. During this time, immune recovery and function are variable and depend on the type of HSCT. Autologous

BOX 58-2 Time Course of Pulmonary Complications After HSCT

Preengraftment (after transplant day 0–30)
Infections (primarily bacterial and fungal > viral and protozoal)
Pulmonary edema
Drug toxicity
Radiation toxicity
Diffuse alveolar hemorrhage
ARDS (caused by chemoradiation injury or sepsis)
Recurrent aspiration (enhanced by oral mucositis)
Pulmonary venoocclusive disease
Acute GVHD

Early postengraftment (posttransplant day 30–100)
Infections (especially viral/CMV)
Engraftment syndrome
Delayed pulmonary toxicity syndrome
Idiopathic pneumonia syndrome
Acute GVHD

Late postengraftment (posttransplant day 100+)
Infections (bacterial, fungal, viral, and protozoal)
Chronic GVHD
Drug-related pulmonary toxicity
Bronchiolitis obliterans
Restrictive/fibrotic lung disease
BOOP

BOX 58-3 Infectious Causes of Pulmonary Infiltrates After HSCT

Bacteria
Staphylococcus aureus
Streptococcus pneumoniae
Haemophilus influenzae
Pseudomonas aeruginosa
Klebsiella
Legionella
Nocardia
Mycobacteria tuberculosis
Atypical mycobacteria

Fungi
Aspergillus
Cryptococcus
Histoplasma capsulatum
Coccidioides immitis
Blastomyces
Fusarium
Zygomycetes (*Mucor, Rhizopus*)
Candida

Viruses
CMV
Respiratory virus (RSV, parainfluenza, influenza A and B, adenovirus)
Herpes family (HSV, VZV, HHV-6, HHV-7)
EBV

Other
Pneumocystis carinii (*P. jiroveci*)
Toxoplasma

recipients recover more rapidly than allogeneic recipients. T-cell responses to alloantigens return to normal, but immunoglobulin levels frequently remain depressed. Viral pathogens cause infections because of poor lymphocyte function, whereas inadequate cellular immunity results in bacterial and fungal pathogens. Noninfectious etiologies are primarily responsible for the pulmonary complications seen during this time, including chronic GVHD, drug-related pulmonary toxicity, bronchiolitis obliterans, restrictive/fibrotic lung disease, and BOOP.

Infectious Complications (Box 58-3)

The overall risk of pulmonary infection in patients receiving HSCT (see Box 58-1) depends on multiple factors, including chemotherapy and radiation-induced neutropenia, lung injury induced by the conditioning regimen, rejection in the form of GVHD, local disruption of host defenses, and intensity of pathogen exposure. In addition, HSCT recipients need to develop a functional immune system from donor-derived cells. Although the production of red blood cells, platelets, and granulocytes occur soon after HSCT, production of lymphocytes (and T cells in particular) is considerably delayed. In the first 2 years after transplant, serious infection occurs in 50% of otherwise uncomplicated transplants from histocompatible sibling donors and in 80–90% of matched unrelated donors or histocompatible recipients who have GVHD develop.

There has been a shift in the microbiology of posttransplant pneumonia over the past two decades, largely in part because of changes in supportive care in the posttransplant period. Prophylactic administration of trimethoprim/sulfamethoxazole, antivirals, antifungals, and fluoroquinolones has decreased the incidence of *Pneumocystis carinii* (*P. jiroveci*, *PCP*), cytomegalovirus (CMV), herpes simplex (HSV), and *Candida albicans* infections. Resistant gram-negative and gram-positive bacteria, viruses, and other fungi remain important pathogens (Box 58-4).

BOX 58-4 Typical Prevention Strategies Against Opportunistic Infections After HSCT

Infections	Prophylaxis
Pneumocystis carinii (jiroveci)	Trimethoprim/sulfamethoxazole
CMV	Ganciclovir
HSV	Acyclovir
Candida sp.	Fluconazole
Aspergillus sp.	Voriconazole
Toxoplasma	Trimethoprim/sulfamethoxazole

Bacterial

Bacterial pneumonia is a major cause of morbidity and mortality in patients receiving HSCT. The first month after transplant is notable for pneumonias caused by usual nosocomial pathogens, with an incidence of ~15%. Bacterial pneumonia is frequently due to *Staphylococcus* and *Streptococcus* species (24% and 13%, respectively, in one series), and gram-negative organisms including *Pseudomonas*, *Klebsiella*, *Escherichia*, *Stenotrophomonas*, *Legionella*, *Acinetobacter*, *Serratia*, *Proteus*, *Enterobacter*, and *Citrobacter* species. Other organisms include

Enterococcus and rare anaerobes such as *Bacteroides* and *Fusobacterium* species. Community pathogens emerge after the immediate posttransplant period. *Haemophilus influenzae* is the most common isolate, followed by *Streptococcus pneumoniae* and *Legionella* species.

Tuberculous and atypical mycobacterial infections are quite uncommon in nonendemic areas, with an overall incidence of *M. tuberculosis* after allogeneic HSCT of only 0.1–0.25%. In a series from Hong Kong, where the prevalence of TB in the general population is 10-fold higher than that of other developed countries, the incidence of post-HSCT tuberculosis was 5.5%. Median time to infection onset is late, occurring at 150–324 days after transplant. Most patients are initially seen with fever, cough, and radiographic infiltrates, and standard treatment is highly effective. Nontuberculous mycobacterial infection is uncommon among HSCT recipients. *M. haemophilum* can be an important pulmonary pathogen after HSCT and should be suspected in patients with skin and joint findings in conjunction with pulmonary infiltrates. Another rare cause of bacterial pneumonia in allogeneic patients is *Nocardia*.

Fungal

Invasive fungal infection is a life-threatening complication of HSCT. Fungal disease should be considered in patients with persistent focal radiographic abnormalities that do not respond to empiric antibiotics and in those with nodular opacities on chest imaging, prolonged neutropenia, corticosteroid use, or a history of prior fungal infections.

Invasive aspergillosis is the leading cause of infectious death, with a mortality of 70–90% in allogeneic recipients despite treatment. The incidence of invasive aspergillosis in allogeneic recipients is 10–15%, with a bimodal distribution of cases. During the early preengraftment period that is characterized by profound neutropenia, both allogeneic and autologous recipients are at increased risk for invasive aspergillosis. Allogeneic patients experience a second period of vulnerability, however, during the postengraftment phase, coincident with the development of chronic GVHD, because of the need for augmented immunosuppression.

Most cases of invasive aspergillosis are limited to the lungs, but sinus and CNS involvement can also be seen. Common presenting symptoms include cough and dyspnea, with fever absent in up to two thirds of patients. Concomitant pleuritic chest pain and hemoptysis are clues. Radiographic findings include single or multiple nodules, cavities, and consolidation. The "air crescent sign" describes a central nodule partially or fully surrounded by air, indicting a sequestrum of necrotic lung tissue that has separated from the surrounding parenchyma. The "halo sign" on CT describes a rim of low attenuation representing edema or hemorrhage that surrounds a pulmonary nodule and is present in >90% of patients with neutropenia with invasive pulmonary aspergillosis.

Intravenous amphotericin B, voriconazole, and caspofungin are available therapies for treatment of invasive aspergillosis. Despite treatment, mortality is still high. Adjunctive surgical resection of localized disease may be beneficial in selected patients but remains controversial.

Candida, *Cryptococcus*, and *Zygomycetes* (including *Mucor* and *Rhizopus*) are also important pathogens. The prevalence of invasive zygomycotic infection is 2% and bears a similar clinical course to that of *Aspergillus*. Zygomycetes are angioinvasive, leading to thrombosis, pulmonary infarction, and hemorrhage, with radiographs showing cavitation and halo sign, and mortality rates are high at 60–80% despite treatment with amphotericin B and surgical resection.

The endemic fungi are encountered less frequently. *Histoplasma* and *Coccidioides* usually occur as reactivation of latent infection. *Blastomyces* usually represents primary disease. Other emerging fungal pathogens reported to cause pulmonary infections include *Fusarium* and *Scedosporium* species.

Viral

Viral infections, particularly CMV pneumonia, are an important cause of morbidity and mortality in the postengraftment period. Mortality from CMV pneumonia in posttransplant patients exceeded 90% until the advent of combination therapy with ganciclovir and intravenous immunoglobulin (IVIG) that improved survival rates to up to 70%.

The use of prophylaxis has not only reduced the incidence but has also delayed the onset of disease. Previously, 35% of CMV infections occurred during the first 100 days after transplant, but now only 6% are occurring in this time frame; infection after the first 100 days has increased from 4% to 15%. Prophylaxis regimens have taken two approaches: universal prophylaxis to all high-risk patients for a defined period after engraftment, and preemptive treatment of patients only after detection of subclinical viremia by PCR assay. Both strategies reduce the risk of early CMV disease and are endorsed by published practice guidelines.

Immunosuppression and delayed reconstitution of cytotoxic T cells places patients receiving HSCT at increased risk for CMV pneumonia. Those at highest risk are seronegative patients who underwent allogeneic transplant from seropositive donors. Other risk factors include viral shedding from other sites, viremia, chronic steroid use, and GVHD. Patients with chronic GVHD are particularly susceptible to late CMV infection because of an increased need for immunosuppression and inherent immunodeficiency as part of the GVHD process.

CMV pneumonia has a nonspecific clinical presentation that includes fever, nonproductive cough, and hypoxia. Chest imaging demonstrates various abnormalities, most commonly bilateral interstitial opacities on chest X-ray, but may also have focal or diffuse consolidation, nodular opacities, and ground-glass opacities on chest CT. A definitive diagnosis relies on demonstrating viral inclusion bodies in lung tissue (which can be difficult on transbronchial biopsy specimens) or detection of virus in BAL fluid by shell vial assay, polymerase chain reaction, or viral culture (in patients with a compatible clinical presentation). Long-term sequelae include bronchiolitis obliterans organizing pneumonia and restrictive lung disease.

Community-acquired viruses such as influenza A and B, parainfluenza, respiratory syncytial virus, and adenovirus can also cause respiratory failure in HSCT recipients, and collectively these are recovered from up to 33% of patients receiving HSCT who are hospitalized with acute respiratory illness, with RSV being the most common. Parainfluenza virus infection causes both upper and lower respiratory tract symptoms and can present as laryngotracheitis, croup, bronchiolitis, or pneumonia. The incidence in allogeneic transplants is >2%, most commonly with serotype 3, which is associated with lower respiratory tract symptoms. There is no seasonal variation to infection with parainfluenza virus serotype 3. In contrast, infection with the other viruses occurs in colder months (late fall to early spring). Respiratory syncytial virus peaks between January and March and is often associated with concomitant

otitis media or sinusitis. Progression to pneumonia occurs frequently, and the mortality of untreated RSV pneumonia approaches 80%. Early treatment with ribavirin and IVIG may decrease pneumonia-related mortality.

Adenovirus is an uncommon cause of pneumonia and can be isolated in 3–5% of patients after HSCT. It affects the upper and lower respiratory tracts, as well as the gastrointestinal and genitourinary systems. Infection usually develops within the first 3 months of transplantation, with a presentation that might include pharyngitis, tracheitis, bronchitis, pneumonitis, enteritis, hemorrhagic cystitis, or disseminated disease. Mortality with pulmonary involvement may exceed 50%.

Other viral infections include HSV, varicella zoster virus, and human herpesviruses 6 and 7. In the absence of prophylaxis, infection with HSV occurs in up to 18% of transplant recipients, with severe pneumonia in 10% and a mortality up to 20%. The incidence of HSV has been markedly reduced by acyclovir prophylaxis. HSV may cause a severe tracheobronchitis associated with endobronchial ulcers. Human herpes virus 6 has been associated with the idiopathic pneumonia syndrome. Epstein–Barr virus infections usually manifest as posttransplant lymphoproliferative disorder, usually as a B-cell lymphoma, thought to be related to T-cell depletion or suppression strategies. Even coronavirus pneumonia has been reported after hematopoietic stem cell transplant.

Others

The incidence of PCP pneumonia has been markedly reduced by trimethoprim-sulfamethoxazole prophylaxis. Prophylaxis is recommended from time of engraftment to 6 months after transplant in all allogeneic recipients and indefinitely for those on augmented immunosuppressive therapy and those with chronic GVHD. PCP presents approximately 60 days after transplantation with cough, dyspnea, fever, and nearly any chest X-ray finding (most commonly, bilateral interstitial and alveolar infiltrates). Diagnostic yield of BAL is near 90%. Despite trimethoprim-sulfamethoxazole, treatment, mortality can be as high as 89% for PCP infections occurring within the first 6 months after transplant versus 40% for late-onset infections.

Toxoplasma infection is uncommon with a lifetime incidence of 0.3%, but in patients with prior cat exposure and positive pretransplant serologic findings, the frequency is as much as 2%. The infection is typically associated with GVHD; develops by reactivation in the first 6 months after transplant; and affects the brain, heart, and lungs. Another rare cause of pulmonary infection in HSCT patients is *Microsporidia*.

Noninfectious Complications (Box 58-5)

BOX 58-5 Noninfectious Causes of Pulmonary Infiltrates After HSCT

- Cardiogenic and noncardiogenic pulmonary edema
- Diffuse alveolar damage (DAD) or drug toxicity
- Idiopathic pneumonia syndrome (IPS)
- Diffuse alveolar hemorrhage (DAH)
- Engraftment syndrome
- Delayed pulmonary toxicity syndrome (DPTS)
- Interstitial pneumonitis or interstitial lung disease
- Bronchiolitis obliterans (BO) or airflow obstruction
- Pulmonary venoocclusive disease
- Posttransplant lymphoproliferatirve disorder (PTLD)
- Bronchiolitis obliterans organizing pneumonia (BOOP)
- Respiratory failure
- Interstitial fibrosis
- Radiation pneumonitis
- Pulmonary cytolytic thrombi
- Pulmonary alveolar proteinosis
- Transfusion related acute lung injury

Pulmonary Toxicity

In the immediate posttransplant period, pulmonary toxicity from prior chemoradiotherapy or the pretransplant conditioning regimen may manifest as fever, dyspnea, cough, hypoxemia, and patchy or diffuse mixed interstitial and alveolar infiltrates on chest radiography. No prospective studies document the efficacy of steroids in this setting, but in clinical practice, prednisone, 1–2 mg/kg/day, is usually used to treat lung toxicity once infection has been excluded.

Pulmonary Edema

Pulmonary edema, both cardiogenic and noncardiogenic, is the most common early posttransplant complication, usually seen in the first month after transplant. Patients may have underlying cardiac dysfunction secondary to previous treatment with high dose cyclophosphamide, anthracycline, and chest irradiation; IV fluids (given for resuscitation, antibiotics, or maintenance therapy) can lead to cardiogenic pulmonary edema. Drug-induced pulmonary toxicity, sepsis, aspiration, blood transfusions, cytokine release during acute GVHD, and hepatic venoocclusive disease can induce noncardiogenic pulmonary edema. There are also reports of cardiac arrest immediately after infusion of autologous marrow, possibly secondary to noncardiogenic pulmonary edema.

Diffuse Alveolar Damage

Diffuse alveolar damage, as the histologic/pathologic correlate of the acute respiratory distress syndrome, can occur after HSCT, usually in the setting of sepsis or in response to treatment with agents known to cause pulmonary toxicity.

Idiopathic Pneumonia Syndrome

Idiopathic pneumonia syndrome (IPS) is a noninfectious form of acute lung injury defined as widespread alveolar injury in the absence of active lower respiratory tract infection (Box 58-6). Published series report an incidence ranging from 2% to 35%, reflecting the relative difficulty in making the diagnosis, because patients with "idiopathic" pneumonia may actually have occult infection (particularly CMV pneumonia) or pulmonary toxicity because of conditioning regimens. Some have reported a trend toward a higher IPS occurrence after allogeneic transplantation, whereas others have shown a relatively equivalent incidence in recipients of allogeneic and autologous HSCT at 7.6% and 5.7%, respectively. Among allogeneic recipients, the incidence of IPS is significantly lower after nonmyeloablative conditioning regimens than traditional high-dose regimens, consistent with the idea that IPS is the result of chemoradiotherapy. Other risk factors include older age, transplantation for malignancy other than leukemia, high-dose conditioning regimens, total body irradiation, and high-grade acute GVHD. Studies in murine models suggest that the etiology involves an alloimmune cytokine storm from myeloablative conditioning, recruitment of inflammatory and immune-effector cells to the lung, release of oxidants and proinflammatory cytokines, and resultant inflammatory lung injury.

BOX 58-6 Diagnostic Criteria for Idiopathic Pneumonia Syndrome

1. Evidence of widespread alveolar injury as evidenced by:
   a. Multilobar infiltrates on routine chest radiographs or CT scans
   b. Symptoms and signs of pneumonia, e.g., cough, dyspnea, rales
   c. Evidence of abnormal pulmonary physiology
      1. Increased alveolar to arterial oxygen gradient (compared with previous, if available).
      2. New or increased restrictive pulmonary function test abnormality.

   – AND –
2. Absence of active lower respiratory tract infection as evaluated by:
   a. Bronchoalveolar lavage or transbronchial biopsy or open lung biopsy negative for infectious pathogens (bacterial, CMV, respiratory syncytial virus, parainfluenza virus, other respiratory viruses, fungi, *Pneumocystis carinii*, and other organisms).
   b. Ideally, a second confirmatory negative test is done 2–14 days after the initial negative bronchoscopy

The median time to onset of IPS ranges from 21 to 50 days after transplantation. Patients are seen with fever, dyspnea, nonproductive cough, hypoxia, and diffuse pulmonary infiltrates. Patients may progress to respiratory failure within a few days. Mortality approaches 75%. Treatment is primarily supportive care. The response to pulse steroids at a dose equivalent of 1–2 mg/kg/day of intravenous methylprednisolone is generally poor and of uncertain efficacy. Novel agents such as etanercept, a TNF-α blocker, are being investigated.

Diffuse Alveolar Hemorrhage (DAH)

(Figure 58-1 and Box 58-7)

Diffuse alveolar hemorrhage (DAH) was first described in 21% of 141 consecutive patients who underwent autologous HSCT who had dyspnea, nonproductive cough, fever, hypoxemia, diffuse alveolar infiltrates, and progressively bloodier return from BAL develop. The mortality in this retrospective series was 80%. Subsequent studies reported a lower incidence at 5%, with no significant differences noted between those undergoing autologous versus allogeneic transplant. Risk factors include age >40, total body irradiation, transplantation for solid tumors, high fevers, severe mucositis, and renal insufficiency. The pathophysiology is not well understood, but infection, thrombocytopenia, and coagulopathy do not seem to be directly implicated. Autopsy specimens show diffuse alveolar damage. DAH, like IPS, is part of a spectrum of acute lung injury induced by conditioning chemotherapy, radiation, and occult infection. Rapid immune system reconstitution has also been theorized to contribute to DAH. Neutrophil influx into the lung may accentuate the injury and precipitate hemorrhage.

Patients usually are seen during the periengraftment period within the first month after transplantation, but up to 42% of patients are seen late, beyond day 30. Symptoms and radiographic findings usually progress within 48 h, and radiographic changes may precede the clinical presentation by several days. Chest X-rays show patchy interstitial or alveolar infiltrates, often with mid-lower lung predominance, which then become diffuse and widespread. Because DAH has an 80–100% mortality with supportive care alone, prompt diagnosis and treatment are crucial. BAL with progressively bloodier aliquots in the return fluid is the classic diagnostic finding (Figure 58-2). Treatment is with methylprednisolone, 500–1000 mg/day for 3–4 days, followed by steroid taper. Better outcomes are associated with early presentation and autologous transplants (~30% mortality) versus those with late-onset hemorrhage or

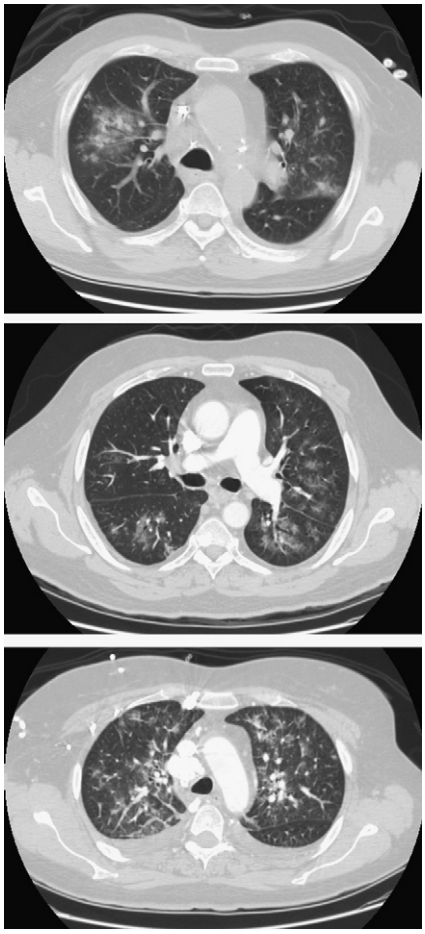

FIGURE 58-1 Representative chest CT images of three individuals who had diffuse alveolar hemorrhage develop (diagnosed by BAL) after hematopoietic stem cell transplantation. Typical findings include bilateral scattered ground-glass opacities that can coalesce with corresponding airspace disease. All microbiology studies (bacterial, fungus, viral, and AFB) were negative.

BOX 58-7 Diagnostic Criteria for Diffuse Alveolar Hemorrhage (DAH)

Evidence for widespread/diffuse alveolar injury as manifested by:
- Multilobar pulmonary infiltrates
- Abnormal pulmonary physiology with increased alveolar to arterial oxygen gradient
- Restrictive ventilatory defect

Absence of infectious etiologies compatible with the diagnosis

Bronchoalveolar lavage (BAL) showing progressively bloodier return from three separate subsegmental bronchi or the presence of blood in at least 30% of the alveolar surfaces of lung tissue

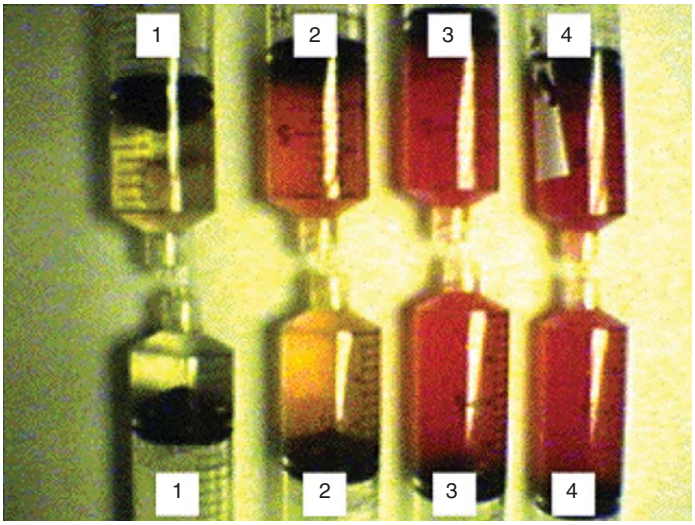

FIGURE 58-2 Bronchoalveolar lavage findings demonstrating diffuse alveolar hemorrhage. Four sequential 20-mL lavages were performed in the RML (*top syringes*) and repeated in the lingula (*bottom syringes*). Each lobe shows increasing bloody return with each sequential lavage, and these findings are consistent with a diagnosis of diffuse alveolar hemorrhage.

allogeneic transplants, in which mortality was 70%. Recombinant factor VIIa may be a useful adjunct.

Engraftment Syndrome (Box 58-8)

The engraftment syndrome is by characterized by fever, rash, and noncardiogenic pulmonary edema that occurs coincident with neutrophil recovery and engraftment. The incidence of engraftment syndrome is 7–11% and occurs most frequently after autologous HSCT. Proposed risk factors include transplantation for breast cancer, use of peripheral blood rather than bone marrow stem cells, and use of granulocyte colony-stimulating factors to mobilize marrow. The etiology is unclear; it may be attributed to increased cytokine release and neutrophil degranulation during engraftment. As in DAH, rapid immune system reconstitution is also theorized. Treatment is 1–2 mg/kg/day of intravenous methylprednisolone followed by a rapid taper.

BOX 58-8 Diagnostic Criteria for Engraftment Syndrome*

Major criteria

Temperature ≥38.3° C with no identifiable infectious etiology.
Erythrodermatous rash involving more than 25% of body surface area and not attributable to a medication.
Noncardiogenic pulmonary edema, manifested by diffuse pulmonary infiltrates consistent with this diagnosis, and hypoxia.

Minor criteria

Hepatic dysfunction with either total bilirubin ≥2 mg/dL or transaminase levels ≥ two times normal
Renal insufficiency (serum creatinine ≥ two times baseline)
Weight gain ≥2.5% of baseline body weight
Transient encephalopathy unexplainable by other causes

*A diagnosis of ES is established by the presence of all three major criteria or two major criteria and one or more minor criteria. ES should occur within 96 h of engraftment (PMN ≥500/μL for 2 consecutive days).

Delayed Pulmonary Toxicity Syndrome

Interstitial pneumonitis and fibrosis developing after high-dose chemotherapy and autologous HSCT for breast cancer is referred to as delayed pulmonary toxicity syndrome (DPTS). This syndrome most often presents between 6 weeks to 3 months after HSCT, is generally responsive to corticosteroid therapy, and has a better prognosis than IPS. Patients are seen with dyspnea on exertion, nonproductive cough, and fever. Pulmonary function tests (PFTs) show a restrictive ventilatory defect and diminished diffusion capacity. DPTS is thought to represent a manifestation of chemotherapy-induced lung injury, because lung biopsy shows alveolar septal thickening, interstitial fibrosis, and type II pneumocyte hyperplasia, all consistent with drug toxicity. Moreover, carmustine (BCNU) and cyclophosphamide, both of which are used in the conditioning regimens that are associated with DPTS, are known to be pneumotoxic.

Interstitial Pneumonitis or Interstitial Lung Disease

Interstitial pneumonitis manifests with diminished diffusing capacity, and total lung capacity is common and can occur at virtually any time after transplantation, with many patients remaining asymptomatic. These PFT changes are usually secondary to treatment with conditioning regimens, particularly those containing carmustine.

Bronchiolitis Obliterans

Chronic airflow limitation caused by bronchiolitis obliterans is the most common late complication of allogeneic HSCT and is exceptionally rare after autologous HSCT. The incidence varies from 6% to 26%, depending on how the airflow limitation is defined. It typically occurs after the third month posttransplant and is associated with underlying chronic GVHD. Other risk factors include older age, lower pretransplant FEV_1/FVC ratio, low serum immunoglobulin levels, methotrexate use, and early posttransplant respiratory viral infections. The etiology is unclear, but its strong association with GVHD suggests an immune-mediated injury induced by donor cytotoxic T cells against host bronchial epithelium. The reported association with methotrexate suggests direct drug-related injury may also play a role.

Patients with bronchiolitis obliterans are seen with insidious onset of nonproductive cough, dyspnea, and wheezing. Chest radiographs are often normal, but high-resolution CT shows air trapping, hypoattenuation, and bronchial dilatation. PFTs show airflow limitation that progresses with time; also, the rate of progression is variable, with some having rapid progression to hypercapnic respiratory failure and death and others having a protracted course. Airflow limitation has been associated with a substantial attributable mortality: 9% and 18% at 3 and 10 years after transplant, respectively. Mortality is higher in the subpopulation of patients who have chronic GVHD (22% and 40% at 3 and 10 years, respectively). Treatment involves augmented immunosuppression and, in some cases, lung transplantation. Azithromycin has been suggested as possible therapy.

Pulmonary Venoocclusive Disease

Pulmonary venoocclusive disease (PVOD) is a rare complication of HSCT characterized by intimal proliferation and fibrosis of pulmonary venules, leading to progressive vascular obstruction and increased pulmonary capillary and arterial pressures. The process is thought to be due to an infectious or toxic injury to the endothelium. Chemotherapeutic agents most commonly associated with PVOD include carmustine, mitomycin C, and bleomycin.

Patients are seen several months after transplantation with progressive dyspnea on exertion and fatigue. They may also have pleural effusions with right upper quadrant tenderness and ascites. The presence of pulmonary arterial hypertension, pulmonary edema, and normal pulmonary artery occlusion pressure strongly suggests the diagnosis. Pulmonary vasodilators can exacerbate the pulmonary edema. Anecdotal reports describe response to high-dose corticosteroids.

Posttransplant Malignancy/ Lymphoproliferative Disorder

Posttransplant lymphoproliferative disorder (PTLD) is another uncommon complication of allogeneic HSCT. It represents an uncontrolled expansion of donor-derived, Epstein–Barr virus–infected B lymphocytes. The overall incidence is 1% but increases to 22% in patients with more than two of the following risk factors: unrelated or HLA-mismatched related donors, T cell–depleted donor stem cells, and use of antithymocyte globulin.

Patients are usually seen within the first 6 months after transplant with lymph node, liver, and spleen involvement, often with relapse with the original malignancy (especially lymphoma) or with secondary lymphomas. Lung involvement is seen in 20% of cases. PTLD is often refractory to standard chemotherapy, and treatment involves administration of anti-B–cell monoclonal antibodies and reduced immunosuppression. Survival is poor, especially for those with underlying hematologic malignancies.

Bronchiolitis Obliterans Organizing Pneumonia

Bronchiolitis obliterans organizing pneumonia (BOOP) occurs as a late complication of HSCT and can be a sequela of treated CMV pneumonitis, related to chronic GVHD, or can be idiopathic. The incidence is 1.3% in adult allogeneic recipients who have survived beyond 3 months. This is often a steroid-responsive lesion, and with treatment long-term survival is 80%.

Respiratory Failure

Respiratory failure occurs commonly after HSCT and is associated with poor outcomes. In a series of >1400 consecutive patients who underwent HSCT at the Fred Hutchinson Cancer Research Center between 1986 and 1990, 23% required mechanical ventilation and only 4% of those survived. Risk factors include older age, active malignancy at the time of transplant, and receipt of HLA-nonidentical allogeneic transplant. Later studies report survival rates of 16–26% in ventilated patients, in part because of the use of peripheral stem cell transplantation and perhaps early institution of noninvasive mechanical ventilation. Uniformly fatal outcomes are seen in patients with multisystem organ failure, especially those with hepatic and renal dysfunction.

Other

Pulmonary cytolytic thrombi (PCT) is the term describing a vasculopathy that occurs in pediatric allogeneic HSCT recipients that is characterized by an obliterative arteriopathy, occlusive vascular lesions, and hemorrhagic infarcts. This entity can resolve spontaneously without specific therapy. Pulmonary alveolar proteinosis has also been reported as a reversible cause of respiratory failure after allogeneic HSCT for acute leukemia.

Diagnostic Evaluation

The approach to evaluation should consider the time frame at which the pulmonary problem is occurring, the radiographic abnormalities, and a number of individual patient factors, such as exposure to cardiopulmonary-toxic drugs during the pretransplant conditioning regimen, a history of receiving chest radiotherapy, current and previous immunosuppression regimens, current and previous prophylaxis for infectious agents, CMV status of donor and recipient, any history of previous opportunistic invasive fungal disease, and exposure to cats, birds, mycobacteria, or endemic fungi. Pulmonary function test abnormalities can provide clues to the underlying disorder, and evidence of a restrictive ventilatory defect on PFTs should be followed by a chest CT to assess for subtle interstitial disease. Sputum examination can also be very useful in identifying certain pathogens. Invasive diagnostic procedures are usually reserved for patients who are stable enough to undergo the procedure and/or who have progressive disease despite initial therapy.

Patterns on Imaging

The chest radiograph can be normal in 15% of symptomatic patients with proven infiltrative lung disease and can miss small nodules, cavitations, radiation pneumonitis, GVHD, and bronchiolitis obliterans. Chest CT is more sensitive than the plain chest radiograph and is often used for localization to guide invasive diagnostic procedures.

Diffuse infiltrates are common and are highly nonspecific. During the preengraftment phase, pulmonary edema is the main cause. Other noninfectious processes include DAH, engraftment syndrome, and drug reactions. After engraftment, infections are the main cause of diffuse infiltrates. Typical chest radiographic findings in viral pneumonia consist of reticulonodular opacities in a peribronchial, perivascular distribution. The most common radiographic findings of CMV pneumonitis after HSCT are parenchymal opacification (90%) and multiple (<5 mm) nodules (29%), but X-rays may be normal in 10%. Noninfectious processes in the postengraftment period include pulmonary edema, DAH, IPS, NSIP, lymphangitic spread of tumor, and chemoradiation-induced pneumonitis.

Focal infiltrates usually reflect infectious processes and have a higher likelihood of yielding a specific diagnosis. Segmental or lobar infiltrates are usually caused by bacterial, fungal, or mycobacterial infections. Localized consolidation accompanied by an ipsilateral pleural effusion suggests bacterial infection. The noninfectious processes associated with focal infiltrates include hemorrhage, pulmonary emboli, acute radiation pneumonitis, and carcinoma.

Nodular infiltrates with or without cavitation are typical of fungal infections, with aspergillosis being the most common (often including the "air crescent" and "halo" signs as described previously). *Nocardia* and *Cryptococcus* also present as nodular masses, the former commonly cavitating. Invasive candidiasis may also present as disseminated nodules, and septic emboli

as nodular infiltrates, with feeding pulmonary vessels and wedged-shaped subpleural lesions representing infarcts.

Pleural effusions suggest bacterial, mycobacterial, or nocardial infections. Noninfectious processes associated with pleural effusions include pulmonary edema, hepatic venoocclusive disease, pulmonary infarction, and malignancy.

Pulmonary Function Tests

Baseline PFTs should be obtained before HSCT, after transplant in symptomatic patients, and at regularly scheduled intervals in high-risk individuals. Pretransplant abnormalities in the diffusion capacity and the alveolar-arterial oxygen difference are independent risk factors for interstitial pneumonitis and death. Reduction in pretransplant FEV_1 is a strong predictor for the subsequent development of CMV pneumonia in CMV-seropositive allogeneic HSCT recipients. After transplant, PFTs abnormalities commonly seen include decline in lung volume, diffusing capacity, and airflow. Posttransplant reduction in DL_{CO} is found in half of the patients and may be persistent from 3 months to several years. Restrictive pattern is reported in 34% of HSCT recipients. The etiology of the restrictive impairment and the reduced DL_{CO} seems to be multifactorial, including toxic effects of chemoradiation, recurrent pulmonary infections, pulmonary edema, generalized muscle weakness, idiopathic interstitial pneumonias, and BOOP.

Invasive Diagnostic Procedures

After radiographs, the next diagnostic step in a patient with a worsening clinical picture is usually an invasive test. Patients with focal infiltrates can often be given a trial of empiric antibiotics, with invasive testing performed several days later if there is no response. Additional testing is discussed in the following text.

Serologic Studies

Aspergillus is the most common invasive fungal infection in posttransplant patients, and noninvasive testing for early diagnosis can alter the posttransplant course. The galactomannan assay (which uses monoclonal antibody directed against galactomannan, a cell wall antigen) detects *Aspergillus* antigen by ELISA and is the only approved serologic marker for *Aspergillus* infection. It can be done on blood and BAL fluid. Early studies showed a sensitivity and specificity >90% with improvement in time to diagnosis. Results can be obtained in 3 h as opposed to the 4 weeks by standard culture methods. Serial monitoring increases the sensitivity and may detect the disease before development of clinical symptoms.

Determining CMV serologic status of both recipient and donor is essential in pretransplant screening, especially because CMV disease in the posttransplant period is one of the most lethal infectious complications. The serologic status of the recipient as opposed to the donor is the primary determinant for CMV conversion. A shell vial culture with monoclonal antibody to p72 requires only 48 h, and tests for antigenemia are rapid, standardized, semiquantitative, and inexpensive. Nucleic acid amplification by PCR on DNA extracted from infected leukocytes also allows rapid diagnosis (detects infection 2 weeks before viral cultures become positive and 1 week before positive antigenemia) and is highly sensitive. CMV pneumonia, once fatal to 15% of allogeneic recipients, has become markedly less common with use of these early detection techniques that allow early treatment.

Pitfalls and Controversies

Bronchoscopy

The efficacy of BAL is highly variable. In different retrospective series BAL had an overall diagnostic yield of 30–60%, with a 4–15% complication rate but only modified treatment in 20–35%. The additional diagnostic value of transbronchial biopsy in conjunction with BAL is likewise controversial. Transbronchial lung biopsy is superior to BAL alone for the diagnosis of malignancy and may yield lung biopsies that are consistent with pulmonary drug toxicity, DAD, or BOOP. However, transbronchial biopsy is not routinely performed in the evaluation of HSCT patients with pulmonary complications because of the attendant risks.

An NIH review on the efficacy of BAL in immunocompromised patients with pulmonary infiltrates found that the procedure was diagnostic in 55% of cases, with the most common finding being infection. The most common pulmonary complications diagnosed were DAH (5%), bacterial pneumonia (23%), RSV (19%), and *Aspergillus* (14%).

A review of 27 bronchoscopies and transbronchial biopsies in breast cancer patients who underwent HSCT found that the diagnostic yield of BAL alone was only 22%, which increased to 71% with transbronchial biopsy. The most common conditions diagnosed were pulmonary drug toxicity (47%), bacterial infection (17%), and invasive aspergillosis (11%). The NIH experience with the diagnostic yield of transbronchial lung biopsy was less positive, with nondiagnostic or negative findings in 47% and 24%, respectively.

Transthoracic Needle Aspiration

The yield of transthoracic needle aspiration (TTNA) under CT or fluoroscopic guidance has a high sensitivity (70%), with the most common findings being infection and malignancy. Pneumothorax is a common complication, however, frequently requiring chest tubes.

Surgical Lung Biopsy

If no diagnosis is made with either bronchoscopy or TTNA, surgical lung biopsy by either open thoracotomy or video-assisted thorascopic approach is considered next and is the diagnostic "gold standard" (60–83% sensitivity) in evaluating pulmonary infiltrates after HSCT. The effect of surgical lung biopsy on patient outcome and survival is still controversial, however. Some studies have shown that patients with surgical lung biopsy had poorer outcomes, that the results rarely led to a change in therapy, and that the patients frequently had complications such as pneumothorax, hemothorax, prolonged mechanical ventilation, wound hematoma and dehiscence, incisional neuritis, and tumor recurrence at chest tube site. The procedure is associated with a postoperative mortality up to 8%. Survival at 30 and 90 days may be increased in patients who have a specific diagnosis. We recommend reserving open biopsy for patients whose underlying condition has a reasonable prognosis and those in whom the results might have a good chance of changing management.

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