Pulmonary and Hepatic Complications of Hematopoietic Cell Transplantation

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5.1 Introduction

Significant advances have been made in allogeneic transplantation for both adult and pediatric transplant recipients over the past 20 years, corresponding with dramatic declines in treatment-related mortality (TRM). The cumulative incidence of TRM at 1 year following unrelated donor transplants has decreased from 40 to 15 % between 1987 and 2006 for children with acute leukemia, the primary indication for transplant in the pediatric population (MacMillan et al. 2008). Improvements in conditioning regimen, supportive care, and human leukocyte antigen (HLA) testing have all been associated with incremental improvements in survival during this period. In particular, the management of both infectious and noninfectious organ complications has changed dramatically, with improved sensitivity for diagnostic testing for pathogens and tremendous improvements in our understanding of organ complications. Two organ complications in particular, pulmonary and hepatic, have been a major focus of investigation over the past several decades. The introduction of tumor necrosis factor (TNF) inhibitors for the management of acute, noninfectious lung injury and the introduction of an endothelial stabilizing agent (defibrotide) for the management of hepatic veno-occlusive disease have been major advances in the field.

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5.2 Pulmonary Complications

5.2.1 Overview

Pulmonary toxicity, both infectious and noninfectious, develops in 25–50 % of hematopoietic cell transplant (HCT) recipients, accounting for nearly 50 % of all transplant-related deaths (Clark et al. 1999; Crawford and Hackman 1993; Weiner et al. 1986; Quabeck 1994; Crawford et al. 1993; Kantrow et al. 1997; Afessa et al. 2001). Despite advances in treating opportunistic organisms, infectious lung injury remains a significant problem, particularly in patients with graft-versus-host disease (GVHD) or in individuals with delayed immune reconstitution. On the other hand, noninfectious lung injury can be either acute or chronic depending upon the time of occurrence posttransplant and the rate of disease progression. Acute lung injury may be alloreactive or non-alloimmune, secondary to cardiogenic shock or chemoradiotherapy effects. Chronic lung injury may be obstructive or restrictive in nature, depending upon the pathogenesis of the lung injury pattern (Holland et al. 1988; Schultz et al. 1994; Crawford et al. 1995; Sullivan et al. 1992; Sanchez et al. 1997; Badier et al. 1993; Quigley et al. 1994). This section will review the definitions, risk factors, and pathogenesis of lung injury occurring after HCT.

5.2.2 Diagnostic Evaluation

Because respiratory distress can progress rapidly once established, the timely coordination of care between the hematology-oncology, pulmonary, and often intensivist teams is essential to optimizing outcomes. Determination of the severity of respiratory dysfunction, including an assessment of the need for supplemental oxygen support, overall fluid balance, renal function, and cardiac output should be followed by radiographic imaging. In general, an initial chest x-ray or CT scan will identify the presence of lobar, multilobar, or diffuse pulmonary infiltrates (Fig. 5.1). While such findings may impact the decision-making process, they are nondiagnostic in and of themselves. In the absence of obvious cardiac failure or iatrogenic fluid overload, bronchoscopy with bronchoalveolar lavage (BAL) should be considered when infiltrates are present. BAL samples should be sent for a number of diagnostic tests to determine the potential presence of community or hospital acquired and opportunistic infections. Besides bacterial, fungal, and cytological stains, quantitative cultures should be performed on BAL fluid for diagnostic purposes. In addition, direct fluorescent antibody stains, centrifugation cultures (shell vial), or polymerase chain reaction (PCR) assays may also be very useful in isolating/identifying various viral pathogens.

The role of BAL in HCT recipients remains a matter of debate, with the diagnostic yield ranging from 31 to 67 % in various reports (Huaringa et al. 2000). In many cases, patients are referred for BAL after several days of symptoms and only after empiric antibiotic therapy has been well established. Empiric antibiotic management has been reported to provide inadequate coverage in over 40 % of patients with pathogens identified on subsequent BAL (Ascioglu et al. 2002; Prasoon et al. 2004). Furthermore, prolonged empiric antibiotics may diminish growth of potential pathogens, limiting the subsequent utility of bronchoscopic procedures. In a retrospective study of 598 patients who underwent BAL within the first 100 days post-HCT at MD Anderson Cancer Center, the overall yield of BAL was 55 %, with the yield 2.5 times greater among patients in whom a BAL was performed within the initial 4 days of clinical presentation. In addition, pneumonia-associated deaths were three times higher (18 % vs. 6 %) in those patients undergoing late bronchoscopy, following 4 days of clinical symptoms (Shannon et al. 2010). Yanik and colleagues examined 444 bronchoscopy procedures completed on 300 patients who received HCT at the University of Michigan from 2001 to 2007 (Yanik et al. 2008a). Only 13 % of BAL specimens collected in the first 30 days of HCT were positive for infection, with the diagnostic yield increasing to 33 % between days 31 and 100. Hence, while the majority of HCT patients requiring BAL

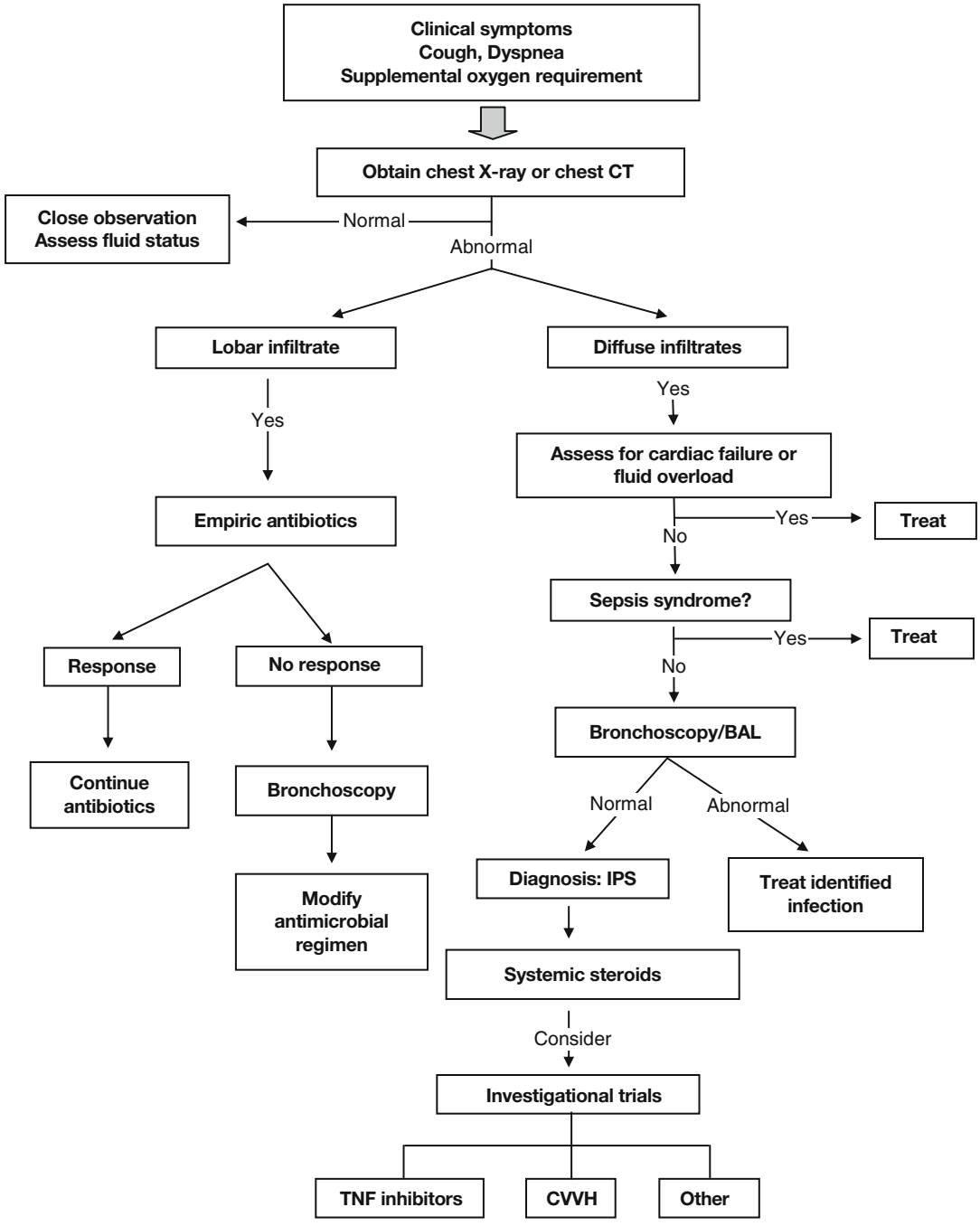


Fig. 5.1 Evaluation of a patient with respiratory dysfunction (*Abbreviations*: *CT* computed tomography, *BAL* bronchoalveolar lavage, *IPS* idiopathic pneumonia syndrome, *TNF* tumor necrosis factor, *CVVH* continuous veno-venous hemofiltration)

within the first 100 days may be categorized as having idiopathic pneumonia syndrome (IPS), a significant number of individuals will have evidence for infection. BAL resulted in changes in medical management in approximately 60 % of cases.

5.2.3 Infectious Lung Injury

Factors contributing to infectious pneumonitis following HCT may include suppression of laryngeal or cough reflexes, impaired removal of respiratory secretions due to decreased mucociliary clearance or airway obstruction, and impaired humoral and cellular defense mechanisms. Quantitative and/or qualitative defects in neutrophil or lymphoid function allow nonpathogenic organisms to ultimately become both invasive and pathogenic. With the lungs of a 10 kg child exposed to approximately 2,000 liters of inhaled air every 24 hours, the number of organic and inorganic particles and potential pathogenic organisms processed by our respiratory tract each day is countless. A fine balance exists between those organisms that become true pathogens and those that remain commensurate and often depends upon the quantity of inoculum received and host-defense factors outlined above.

Infectious pneumonitis may be subdivided into those associated with either interstitial or parenchymal involvement. Common pathogens that cause interstitial pneumonitis include community-acquired respiratory viruses (e.g., parainfluenza, respiratory syncytial virus (RSV), influenza, metapneumonia), mycoplasma, and opportunistic pathogens such as *Pneumocystis jiroveci* (PCP), whereas bacterial and fungal pathogens are more frequently associated with parenchymal changes.

CMV pneumonitis remains a significant cause of morbidity and mortality following allogeneic HCT. In the absence of a CMV prevention strategy (e.g., preemptive monitoring of CMV by plasma PCR for antigenemia or universal prophylaxis), CMV pneumonitis may develop during the first 100 days following HCT with a peak incidence at approximately 8 weeks. In the current era, most CMV infections occur after the monitoring or prophylaxis period ends. CMV pneumonitis in patients with chronic GVHD has also been well documented (Boeckh and Ljungman 2002; Osarogiagbon et al. 2000). With the availability of improved antiviral therapy, the mortality rate associated with CMV pneumonitis has declined significantly in recent years (Reusser 1991). Risk factors for the development of CMV disease include the presence of acute GVHD, recipient CMV seropositivity, transplantation for a hematologic malignancy, and the use of antithymocyte globulin during the transplant process (Osarogiagbon et al. 2000; Ljungman et al. 2003). Radiological manifestations of CMV range from diffuse interstitial opacities to widespread air space consolidation (Shimada et al. 2004). Histopathology remains the gold standard for identification of CMV pulmonary disease. Though molecular techniques have an excellent sensitivity for detection of infection, they may be less specific in regards to identifying CMV pneumonitis. The potential for polymicrobial superinfections is another concern in the transplant patient with CMV pulmonary disease, given the multiple issues often involved in patients with active CMV infections, including the concurrent use of systemic corticosteroids and prolonged empiric antibiotic usage.

Respiratory syncytial virus (RSV) is a single-stranded, enveloped RNA virus that presents as a self-limiting upper respiratory tract infection in immunocompetent individuals or a potentially fatal pneumonitis in immunocompromised patients (Ebbert and Limper 2005). Outbreaks in patients undergoing allogeneic HCT have been associated with mortality rates as high as 78 % (Englund et al. 1988; Harrington et al. 1992). In the United States, the onset of RSV infections typically begins in November and continues for approximately 24 weeks. The organism is highly contagious, with transmission occurring primarily through surfaces contaminated with viral-laden nasal or oral secretions. Even in immunocompetent patients, native memory responses are incomplete, allowing for repeated infections. The overall virulence of this agent places the immunocompromised patient at particular risk for fatal lower respiratory tract infections during the seasonal period (Ebbert and Limper 2005). Radiographically, patchy alveolar or diffuse interstitial infiltrates may be seen. Clinically, affected patients may exhibit profound dyspnea and hypoxemia, with or without concurrent upper respiratory tract symptoms. Less than 50 % of patients with lower tract involvement have preceding or concurrent

nasopharyngeal symptoms (Ebbert and Limper 2005; Harrington et al. 1992). The use of aerosolized ribavirin (6 g/day) using small particle generators has resulted in a decrease in RSV shedding, but clinical efficacy has not been proven (Ebbert and Limper 2005; Boeckh et al. 2007). Palivizumab may be considered as prophylaxis option in adults with lower respiratory tract disease (Hynicka and Ensor 2012).

The clinical impact of recently described viruses including human metapneumovirus and non-SARS human coronaviruses is not yet clear. Human metapneumovirus (hMPV) is a paramyxovirus recently recognized as the first human pathogen within the genus *Metapneumovirus* (van den Hoogen et al. 2004). The virus was first identified in the Netherlands in 2001 and was recently reported as a potential pathogen in allogeneic transplant recipients (Englund et al. 2006). In the bone marrow transplant setting, infected patients typically present within the first 50 days posttransplant and exhibit clinical and radiographic findings similar in appearance to IPS. Rapid progression of respiratory symptoms may occur, with a median of 4 days reported between initiation of oxygen support and death (Englund et al. 2006). The clinical spectrum of hMPV as a cause of interstitial pneumonia posttransplant remains ill defined, with issues such as the frequency of asymptomatic shedding, improved detection methods, and treatment strategies all under investigation.

The reactivation of latent viruses, especially herpes family and adenovirus, may also clinically mimic interstitial pneumonitis (Shields et al. 1985). However, in the vast majority of cases, clinical symptoms related to systemic involvement are manifested by signs of disease in other organs, including abdominal pain, elevation of serum hepatic transaminases with CMV, varicella zoster virus, or adenovirus, and oral mucosal involvement with herpes simplex viruses.

Bacterial pneumonia typically presents as alveolar and parenchymal filling infiltrates, with concurrent fever and clinical symptoms (chest pain, tachypnea, cough). Pneumonias due to bacteria are common in the pre-engraftment period, including infections from both Gram-positive (*Staphylococcus* and *Streptococcus* species) and a wide range of Gram-negative organisms. Factors that impact the risk of early bacterial pneumonia include oral-pharyngeal mucositis, focal or diffuse enteritis, aspiration risk due to the influence of opiates and sedatives, and catheter-related risks. Pneumonias due to Gram-negative organisms *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Acinetobacter*, *Escherichia coli*, and *Enterobacter* have all been commonly reported within the first 100 days posttransplant, of particular concern in patients with concurrent gastrointestinal GVHD (Martin-Pena et al. 2011). Later onset bacterial pneumonias (following day 100 post-HCT) are not uncommon in patients with concurrent chronic GVHD, especially prominent in patients with bronchiolitis obliterans syndrome (BOS) or those on systemic corticosteroids for chronic GVHD management.

Fungi are historically classified as either yeasts (*Candida*, *Trichosporon*, *Cryptococcus*) or molds, with molds subdivided by septate hyphae (*Aspergillus*, *Scedosporium*, *Fusarium*, *Histoplasma*, *Penicillium*) or aseptate hyphae (*Mucor*, *Rhizopus*). Fungi rarely cause acute infections in the immunocompetent host. *Candida* species, for example, are commensal flora of the nasopharyngeal tract and skin, rarely causing lower respiratory tract invasion in the immunocompromised host. Candidal infections and candidemia are commonly seen when breakdowns in epithelial and mucosal barriers occur in conjunction with concurrent use of empiric antibacterial agents that eradicate normal bacterial flora. Tissue cultures are required to establish the diagnosis of invasive *Candida*, with both bronchoalveolar lavage and sputum cultures poor predictors of invasive pulmonary candidal infections. In contrast, invasive fungal infections from pathogenic molds are a common cause of pneumonia in the posttransplant setting, with invasive *Aspergillus* infections occurring in 10–15 % of allogeneic transplant recipients. *Aspergillus* pneumonia has been reported at a median 92 days posttransplant, and overall survival from invasive *Aspergillus* has been reported at less than 30 % (Grow et al. 2002). Risk factors for the development of *Aspergillus* pneumonia include prolonged corticosteroid usage (≥1 mg/kg/day), history of recent

cytomegalovirus (CMV) infection, and prolonged neutropenia (Grow et al. 2002; Garcia-Vidal et al. 2008). The combination of neutropenia, impaired T-cell function, and abnormal glucose metabolism is an additive risk for invasive fungi. Definitions of invasive fungi were established in 2002 to distinguish colonization from actual infection. Invasive fungal infections are now classified as proven, probable, or possible. Proven infections require histologic confirmation or a positive tissue culture. Probable infections require both a host factor and clinical and/or fluid cultures consistent with an invasive fungus (De Pauw et al. 2008). Currently available tests for the serum fungal markers beta-glucan and galactomannan could also be useful to differentiate colonization from invasive infections with *Candida* and *aspergillus* species, respectively. Radiographic features of invasive fungi are heterogenous, with small and large nodules, ground-glass opacifications, cavitary lesions, tree-in-bud appearance, and halo signs can be observed on chest radiograph or computed tomography (CT). Treatment of invasive fungi makes use of the unique biology of the organism. Fungi contain a cell membrane with ergosterol and a cell wall with beta-glucan, both targets for antifungal therapy. Voriconazole provides effective therapy for a wide range of pathogenic fungi, excluding *Mucor* species. Both posaconazole and lipid formulations of amphotericin B provide coverage for *Mucor*, in addition to coverage for *Aspergillus* and *Candida* species. The clinician initiating voriconazole or other antifungal "azole" therapy should be mindful of its impact on cytochrome p450-dependent drugs, including the calcineurin inhibitors tacrolimus and cyclosporine and the mTor inhibitor sirolimus. When voriconazole is initiated, doses of tacrolimus and cyclosporine should be reduced by 50 %, with even greater dosing reduction (90 %) for sirolimus if being given in conjunction with voriconazole.

5.2.4 Noninfectious Lung Injury

Noninfectious lung injury may be mediated by either alloimmune or non-alloimmune mechanisms. Common alloimmune lung complications post-HCT include IPS, transfusion-related lung injury (TRALI), diffuse alveolar hemorrhage (DAH), or peri-engraftment respiratory distress syndrome (PERDS), existing as a subset of IPS, with both DAH and PERDS existing as a subset of IPS. Non-alloimmune conditions may include the direct cytotoxic effects of conditioning therapy and cardiogenic causes of pulmonary edema.

5.2.4.1 Chemotherapy-Related Pneumonitis

Initially described in the 1970s, chemotherapy-associated pulmonary toxicity has been reported in association with multiple chemotherapeutic busulfan agents, including BCNU, busulfan, cyclophosphamide, and melphalan. In particular, BCNU-related lung injury is acute in onset and develops within the first 3 months following HCT in 10–40 % of patients receiving this therapy (Aronin et al. 1980). Clinically, BCNU-related lung injury is associated with a nonproductive cough with increasing dyspnea in the context of rapidly progressing, bilateral, interstitial infiltrates on both chest radiographs and CT. Pulmonary function testing reveals a restrictive pattern of lung injury, with diminished forced vital capacity and total lung capacity noted (Lane et al. 2012). The pathogenesis of BCNU-related lung injury has been ill defined, though increased production of fibrogenic factors such as platelet-derived growth factor-β, insulin-like growth factor I, and transforming growth factor-β1 has been implicated (Shen et al. 2004). Treatment with pulsed doses of corticosteroids early in the clinical course significantly decreases the morbidity and mortality associated with this condition and is key for successful outcomes; if untreated or recognized late in its clinical course, severe pulmonary fibrosis may develop (Shen et al. 2004).

Busulfan, either alone or in combination with other cytotoxic agents, has also been implicated in posttransplant lung dysfunction. However, the use of pharmacokinetic targeting of busulfan dosing has decreased the incidence of acute lung injury. Similar to BCNU administration, increased pulmonary toxicity has been noted in patients receiving prior mediastinal radiotherapy, following either autologous or allogeneic HCT (Bolling et al. 2009).

5.2.4.2 Transfusion-Related Acute Lung Injury (TRALI)

TRALI is one of the leading causes of mortality following infusions of plasma-containing blood products, estimated to occur in 1:1,000 to 1:5,000 transfusions (Silliman et al. 2003; Kopko et al. 2002). All plasma-containing blood products, including whole blood, packed red blood cells (PRBC), fresh frozen plasma (FFP), platelets, cryoprecipitate, granulocytes, immune globulin infusions, and stem cell products, have been linked with the development of TRALI, with albumin the sole exception (Swanson et al. 2006). The diagnosis is based upon clinical symptoms with acute onset of dyspnea and respiratory distress typically occurring 1–6 hours after transfusion. Chest radiographs reveal diffuse pulmonary infiltrates reflecting edema from increased pulmonary vascular permeability. Pathologically, neutrophil infiltrates and overexpression of neutrophil-related cytokines and chemokines have been linked to its development. With mortality rates approximating 5–10 %, TRALI accounts for 47 % of all transfusion-related deaths. Treatment is generally supportive. Discontinuation of the blood product, corticosteroid administration, forced diuresis, and respiratory support results in recovery within 3–4 days in the majority of patients. In over 70 % of cases, donor antibodies directed against HLA class I or II epitopes on recipient hematopoietic cells have been identified as the primary cause of the TRALI event, but in rare cases the antibody may be present in the recipient's plasma and may be directed against transfused donor leukocytes (Kopko et al. 2003; Kao et al. 2003) The use of high plasma volume blood products from alloimmunized donors, including apheresis stem cell products and platelets, is associated with high risk for the development of TRALI (Reesink et al. 2012).

5.2.4.3 Idiopathic Pneumonia Syndrome

IPS refers to an acute lung injury that occurs post-HCT, associated with diffuse alveolar damage in the absence of lower respiratory tract infection. In 1993, a National Institute of Health (NIH) workshop proposed a broad definition for IPS, the definition recently updated by an American Thoracic Society research statement (Table 5.1) (Clark et al. 1993). IPS encompasses a spectrum of disorders, including diffuse alveolar hemorrhage (DAH), peri-engraftment respiratory distress syndrome (PERDS), acute idiopathic interstitial pneumonitis, and chemotherapy-related lung injury. The diagnosis, however, is often one of exclusion, with infectious pneumonitis, sepsis syndrome, cardiac

Table 5.1 Idiopathic pneumonia syndrome: diagnostic criteria

I. Diffuse alveolar injury
(a) Diffuse infiltrates on chest radiograph or computed tomography
(b) Clinical signs of pneumonia (cough, dyspnea, tachypnea)
(c) Evidence of abnormal pulmonary physiology
1. Increased alveolar to arterial oxygen difference
2. New or increased restrictive pulmonary function test abnormality
II. Absence of infectious pneumonitis, as determined by
(a) Bronchoalveolar lavage negative for significant bacterial pathogens, including acid-fast bacilli, *Nocardia*, and *Legionella* species.
(b) Bronchoalveolar lavage negative for pathogenic nonbacterial organisms
1. Viral and fungal culture
2. Shell vial culture for cytomegalovirus (CMV) and respiratory syncytial virus (RSV)
3. Cytology for viral inclusions, fungi, and Pneumocystis jiroveci
4. Direct fluorescence staining with antibodies against CMV, RSV, herpes simplex virus (HSV),varicella zoster virus (VZV), influenza virus, parainfluenza virus, adenovirus, and other organisms
(c) Other organisms/tests to consider
1. Polymerase chain reaction (PCR) for human metapneumovirus, rhinovirus, coronavirus, and human herpesvirus (HHV)6
2. PCR for *Chlamydia*, *Mycoplasma*, and *Aspergillus* species
3. Serum galactomannan ELISA for *Aspergillus* species
(d) Transbronchial biopsy, if condition of the patient permits
III. Absence of cardiac dysfunction, acute renal failure, or iatrogenic fluid overload as etiology for pulmonary dysfunction

Adapted from Panoskaltis-Mortari et al. (2011)

failure, and iatrogenic fluid overload all potentially exhibiting similar clinical presentations.

The cumulative incidence of IPS in the first 120 days after allogeneic HCT ranges between 2 and 15 %, with a median onset 14–42 days post-HCT and mortality rates 50–80 % within 28 days of diagnosis (Panoskaltsis-Mortari et al. 2011; Fukuda et al. 2003; Sakaguchi et al. 2012; Yanik et al. 2008b). IPS has been reported in 8.0 % of pediatric allogeneic transplants, with median onset at 67 days posttransplant (Sakaguchi et al. 2012). Long-term survival for affected children is poor, with TRM significantly higher in affected than non-affected patients (5-year TRM: 52 % vs. 13 %, $p = 0.001$) (Sakaguchi et al. 2012).

Diffuse alveolar hemorrhage (DAH), a subset of IPS, generally develops at the time of neutrophil recovery in the early post-HCT period in the immediate post-HCT period and is characterized by progressive shortness of breath, cough, and hypoxemia with or without fever (Afessa et al. 2001; Robbins et al. 1989; Lewis et al. 2000; Metcalf et al. 1994). Classically, DAH is defined by the demonstration of progressively bloodier aliquots of BAL fluid on successive saline lavages, but frank hemoptysis is rare (Robbins et al. 1989). Mortality from DAH may be as high as 75 % despite aggressive treatment with systemic corticosteroids, with death usually occurring within weeks of diagnosis (Lewis et al. 2000). A small case series has suggested that high dose solumehol (1 gm/day) could be an effective treatment of DAH (Chao et al. 1991). A retrospective study has suggested that the addition of aminocaproic acid to high dose corticosteroids could be of benefit in the treatment of DAH (Wanko et al. 2006). Some patients with DAH can have microorganisms isolated from blood, BAL fluid, or tracheal aspirate within 1 week of alveolar hemorrhage. Majhail and colleagues compared patients with DAH and infection-associated alveolar hemorrhage who presented with similar clinical and radiographic findings in the setting of progressively bloodier BAL fluid following allogeneic HCT (Majhail et al. 2006). Alveolar hemorrhage from either infectious or noninfectious causes has extremely poor outcome following therapy with conventional agents, including steroids (Majhail et al. 2006).

Peri-engraftment respiratory distress syndrome (PERDS) also falls within the definition of IPS (Afessa et al. 2001). PERDS is characterized by fever, dyspnea, and hypoxemia that, by definition, occurs within 5–7 days of neutrophil engraftment (Capizzi et al. 2001; Wilczynski et al. 1998; Bhalla et al. 2000). Although PERDS after autologous HCT appears similar to IPS after allogeneic HCT with respect to clinical presentation and time of onset, PERDS/IPS following autologous transplantation differs sharply from PERDS/IPS in the allogeneic setting, with significantly improved outcomes in the autologous setting (Kantrow et al. 1997; Yanik et al. 2002; Cahill et al. 1996; Capizzi et al. 2001).

Potential etiologies and risk factors for IPS include direct toxicity from HCT conditioning regimen, occult pulmonary infections, and immunologic factors related to acute GVHD (Crawford et al. 1993; Weiner et al. 1989; Kantrow et al. 1997; Atkinson et al. 1991; Della Volpe et al. 2002; Crawford and Hackman 1993; Sakaguchi et al. 2012). In particular, the cumulative incidence of IPS is significantly less following the use of reduced intensity conditioning regimen when compared to conventional, myelo-ablative regimen (Fukuda et al. 2003). Acute GVHD often precedes IPS, suggesting a possible causal relationship between the two disorders (Crawford and Hackman 1993; Bortin et al. 1989; Beschorner et al. 1978; Weiner et al. 1986; Crawford et al. 1993; Kantrow et al. 1997; Afessa et al. 2001). However, although IPS may correlate with the presence of acute GVHD, it does not necessarily correlate with the severity of GVHD, consistent with clinical reports of IPS in allogeneic HCT recipients whose signs and symptoms of GVHD were mild or absent (Yanik et al. 2002; Schultz et al. 1994; Curtis et al. 1995; Clark et al. 1987; Holland et al. 1988; Schwarer et al. 1992).

Historically, the lung has not been recognized as a classic target organ for GVHD, and the specific role of alloreactive donor T-lymphocytes in the pathogenesis of IPS is under considerable debate. Epithelial apoptosis is usually attributed to T-cell-mediated injury and is considered pathognomonic for acute GVHD. Although identified in the lungs of many patients with IPS

(Yousem 1995; Beschorner et al. 1978), epithelial apoptosis has not been consistently observed in allogeneic HCT recipients with lung dysfunction. Based upon murine models, the pathogenesis of IPS appears to be a complex interplay between soluble inflammatory mediators (Th1 cytokines, lipopolysaccharide (LPS), inflammatory chemokines), donor-derived effector T cells, accessory cells (myeloid, pulmonary macrophages), and resident epithelial and endothelial cells. Significant increases in the total number of lymphocytes, macrophages, and neutrophils in the bronchoalveolar space (Cooke et al. 1996), increased vascular permeability, plus elevated levels of TNFα and inflammatory cytokines have been noted in the lung tissue and BAL fluid in both murine models and from clinical samples from patients with IPS (Clark et al. 1998; Shankar and Cohen 2001; Cooke et al. 1996, 2000b; Piguet et al. 1989a). A direct role for TNFα in the development of IPS has been established using strategies that either neutralize its effects (Piguet et al. 1987; Cooke et al. 2000b) or use TNFα-deficient mice as HCT donors (Cooke et al. 2000a; Hildebrandt et al. 2004). Administration of rhTNFR-Fc, a soluble, dimeric, TNF-binding protein at the time of endotoxin challenge in mice, effectively prevents IPS-associated lung injury in this setting (Cooke et al. 2000b). Studies using genetically altered mice have shown that IPS is dependent upon donor-derived, rather than host-derived, TNFα. While TNFα from both donor accessory cells (macrophage/monocytes) and T cells significantly contributes to lung injury, the T-cell component (of TNFα) predominates (Hildebrandt et al. 2004).

TNFα likely contributes to the development of IPS through both direct and indirect mechanisms. In addition to being directly cytotoxic, TNFα increases expression of inflammatory chemokines (Hildebrandt et al. 2004) and major histocompatibility complex (MHC) antigens, modulates leukocyte migration, and facilitates cell-mediated cytotoxicity, including endothelial cell injury, a common feature of IPS (Gerbitz et al. 2004). Strategies that neutralize TNFα in experimental models do not completely abrogate lung injury (Piguet et al. 1987, 1989b; Cooke et al. 2000b; Clark et al. 2000; Hildebrandt et al. 2004), suggesting that other inflammatory and cellular mechanisms besides TNFα may also contribute to the development of IPS. For example, IL-1β, nitric oxide, and reactive oxygen species have also been implicated in the development of lung injury after HCT, particularly in the setting of myelo-ablative conditioning (Haddad et al. 1999; Panoskaltsis-Mortari et al. 1997; Qureshi et al. 2004). An analysis of plasma and BAL fluid protein profiles in patients with IPS showed that in addition to increases in the levels of TNFα and its soluble receptors (TNFR1), significant elevations in other Th1 cytokines (γ-interferon, IL-6) and proteins involved in the LPS cascade (sCD14, LBP) along with several inflammatory chemokines (IL-8, MCP-1, MIG) that regulate leukocyte recruitment to sites of inflammation were also evident (Yanik et al. 2008b).

Treatment options for IPS have historically combined supportive care measures, including supplemental oxygen support, diuretics, broad-spectrum antimicrobial agents, and intravenous corticosteroids (Kantrow et al. 1997; Yanik et al. 2002, 2008b; Tizon et al. 2012). High-dose corticosteroid therapy (>2 mg/kg/day of methylprednisolone equivalent) has not been shown to improve outcome when compared to lower doses of corticosteroids (≤2 mg/kg/day) (Fukuda et al. 2003). More recently, the role for TNF inhibition in the management of IPS has been under investigation. A pilot study from the University of Michigan examined the use of a soluble TNF-binding agent, etanercept, in the treatment of patients who met the diagnostic criteria for IPS. A 4-week course of therapy was given, with a strict definition used to define response (complete cessation of all oxygen support within 28 days of therapy onset). Responses were noted in ten (67 %) subjects, with survival 73 % within the therapy period (Fukuda et al. 2003; Yanik et al. 2008b). A retrospective review of 39 patients treated with either corticosteroids alone ($n=22$) versus corticosteroids plus etanercept ($n=17$) similarly noted high response rates in the etanercept arm. Overall survival was significantly higher in those patients treated with

corticosteroids plus etanercept, both at 28 days (88.2 % vs. 36.4 %, <0.001) and 2 years (18 % vs. 9.1 %, $p=0.003$) following onset of IPS (Tizon et al. 2012). Advances in supportive care, including the early institution of continuous veno-venous hemofiltration, may provide additional help in improving survival, but prospective studies addressing the treatment of IPS with clinical trials are in progress. Based upon these encouraging results, larger phase II (pediatric) and phase III (adult) trials have recently been completed within the Bone Marrow Transplant Clinical Trials Network (phase III) and the Children's Oncology Group (phase II).

5.2.4.4 Bronchiolitis Obliterans Syndrome

Bronchiolitis obliterans syndrome was initially described in the 1980s as a form of chronic lung injury following allogeneic transplant and remains one of the most perplexing posttransplant conditions to manage (Holland et al. 1988; Crawford et al. 1995). The clinical course is highly variable, ranging from a gradual decline in lung function over years to a rapid deterioration over several months. The incidence of BOS has varied from 2 to 25 % following allogeneic HCT, the wide range likely reflecting the nonuniform diagnostic criteria used to define the condition (Afessa et al. 2001; Williams et al. 2009). The disorder is associated with airflow obstruction on pulmonary function testing (PFT) with declines in forced expiratory volume in 1 s (FEV1) and FEV1/forced vital capacity (FVC) ratio required for diagnostic purposes. In early stages, BOS is characterized by small airway inflammation with lymphocytic bronchitis, ultimately progressing to fibrinous obliteration of bronchiolar lumen (Schwarer et al. 1992; Urbanski et al. 1987; Cooke and Yanik 2009).

Respiratory symptoms include cough, dyspnea, and wheezing, but many patients remain asymptomatic despite showing signs of moderate to severe airway obstruction on PFTs (Clark et al. 1987; Holland et al. 1988). Chest radiographs are most often normal except for signs of hyperinflation (Curtis et al. 1995; Holland et al. 1988; Schwarer et al. 1992). Likewise, chest CT findings range from normal early in the course of disease to extensive peribronchial inflammation and bronchiectasis with significant air trapping and diffuse parenchymal hypoattenuation at later time points (Schultz et al. 1994; Ooi et al. 1998). One study has demonstrated that on high resolution CT scanning, BOS is characterized by central airway dilation, the degree of which correlates with decrement in lung function, and is distinct from the central airway narrowing observed with emphysema or asthma (Gazourian et al. 2013). The clinical course of BOS varies from mild to severe with necrotizing bronchiolitis and a rapid decline in respiratory function (Holland et al. 1988; Schultz et al. 1994; Sullivan et al. 1992; Sanchez et al. 1997; Curtis et al. 1995; Clark et al. 1989).

In 2005, a NIH Consensus statement on the diagnosis and staging of chronic GVHD included strict diagnostic criteria for BOS, with subsequent proposed modifications for improved identification of BOS patients (Williams et al. 2009; Filipovich et al. 2005) (Table 5.2). Studies published prior to the 2005 publication used various definitions of disease and response to therapy, making it difficult to translate previous results in the current era. The Fred Hutchinson Cancer Research Center recently utilized the NIH criteria to identify the incidence, risk factors, and mortality from BOS following allo-

Table 5.2 NIH bronchiolitis obliterans syndrome (BOS) diagnostic criteria

No active infection
FEV_1 <75 % predicted or >10 % decline from pre-HCT value
Signs of obstruction
FEV_1/FVC ratio <0.7 or FEV1/SVC ratio <0.7
RV >120 % predicted
RV/TLC >120 %
HRCT with evidence of air trapping
Another manifestation of chronic GVHD in another organ

Adapted from Williams et al. (2009)
NIH National Institutes of Health, *GVHD* graft-versus-host disease, *FEV1* forced expiratory volume in 1 second, *FVC* forced vital capacity, *SVC* slow vital capacity, *RV* residual volume, *TLC* total lung capacity, *HRCT* high-resolution computed tomography

geneic HCT (Au et al. 2011). The overall incidence of BOS was 5.5 % and as high as 14 % in patients with chronic GVHD. The median time to diagnosis was 439 days post-HCT, with chronic GVHD present in 100 % of patients identified with BOS. Lower baseline FEV1 (<80 %) and circulating IgG levels were predictive of BOS onset. Previously reported risk factors for BOS, including busulfan-based regimen, peripheral stem cells as the donor source, methotrexate for GVHD prophylaxis, viral pneumonitis post-HCT, HLA mismatch, disease status, and the use of a myelo-ablative regimen, were not predictive of BOS in this report (Holland et al. 1988; Schultz et al. 1994; Clark et al. 1987, 1989; Chien et al. 2003, 2005). Unfortunately, whereas risk factors for BOS have been identified, no clear predictors of outcome have been reported.

Therapy for BOS remains challenging, with no recognized standard therapy. Once established, the prognosis of BOS is very poor, with 5-year survival rates of 15 % (Chien et al. 2010). Even answers to seemingly basic questions have yet to be determined. At what point should therapy be started? Are BAL, transbronchial, or surgical lung biopsies required prior to starting treatment? How should response be defined? A European GVHD consensus conference (2009) summarized diagnostic criteria and treatment options for pulmonary manifestations of chronic GVHD, with a particular focus on BOS (Hildebrandt et al. 2011). PFTs were recommended pre-HCT, every 3 months for the first 2 years posttransplant, and every 6 months thereafter. When obstructive changes are noted on PFTs, then high-resolution computed tomography (HRCT) with inspiratory and expiratory images is recommended to assess for radiographic signs of BOS, including air trapping, bronchial wall thickening, and bronchiectasis (Fig. 5.2). The degree of obstructive changes (decline in FEV1) that would warrant a HRCT was not specified, though at many centers a 10 % decline in FEV1 would typically initiate a HRCT, especially if the FEV1 was <80 % predicted.

Systemic and topical (inhaled) corticosteroids, mTOR inhibitors, extracorporeal photopheresis (ECP), imatinib, azithromycin, montelukast, and combination topical corticosteroid-bronchodilators have all been utilized with varying degrees of success (Hildebrandt et al. 2011). Few BOS treatment options have been based upon prospective clinical trials (Ratjen et al. 2005; Khalid et al. 2005; Couriel et al. 2006; Yanik et al. 2012). Systemic and topical corticosteroids have become commonplace in managing BOS, supported by small case reports and observational studies (Ratjen et al. 2005; Ishii et al. 2000; Bergeron et al. 2007; Bashoura et al. 2008). Three retrospective studies support the use of inhaled corticosteroids

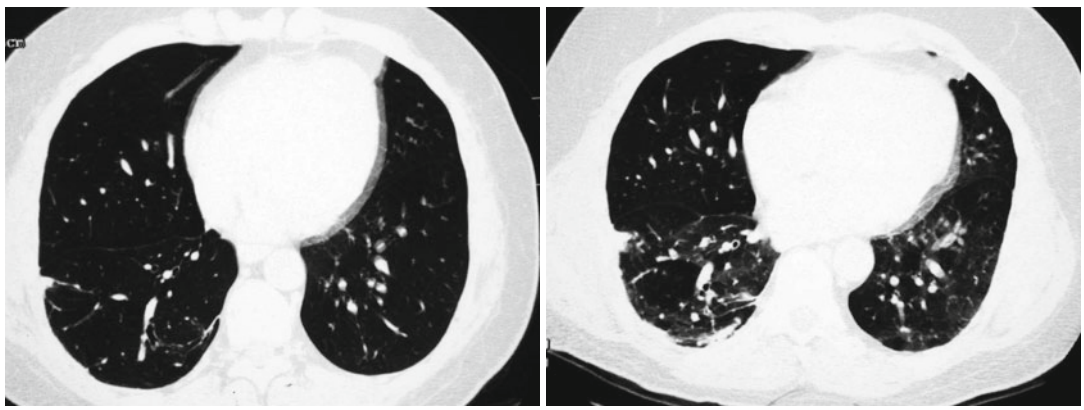


Fig. 5.2 Computed tomography (CT) of bronchiolitis obliterans syndrome (BOS), inspiratory and expiratory films. Note bronchiectasis on both inspiratory and expiratory images

(Bergeron et al. 2007; Bashoura et al. 2008; Norman et al. 2011). The combination of systemic plus inhaled corticosteroids has been examined in a few studies. In one trial, repetitive courses of oral methylprednisolone (10 mg/kg/day) plus inhaled budesonide led to disease stabilization in 7 of 9 patients (Ratjen et al. 2005). The combination of an inhaled steroid plus long-acting bronchodilator (budesonide/formoterol) was reported in 13 patients with BOS, with clinical improvement noted in all 13 patients; responses were seen at a mean 2.3 months following onset of therapy (Bergeron et al. 2007). In another case series, the use of inhaled fluticasone, azithromycin, and montelukast (FAM) therapy was useful in "sparing" systemic corticosteroid usage in eight patients with BOS (Norman et al. 2011). The Chronic GVHD Consortium has begun enrolling patients into a clinical trial investigating the use of FAM therapy for newly diagnosed BOS (NCT01307462).

The use of macrolide antibiotics (azithromycin) for frontline therapy of BOS is widespread in the transplant community, though based upon a single report of eight HCT patients receiving a 12-week course of therapy (Khalid et al. 2005). Subjects did not undergo pre-therapy BAL, thus questioning whether subsequent responses were secondary to anti-inflammatory or antimicrobial effects of the agent. There are no published reports justifying the use of azithromycin for BOS prevention. In an observational study of 81 patients with BOS following lung allografts, 24 of 81 (30 %) experienced an improvement in FEV1 after 6 months of azithromycin therapy (Gottlieb et al. 2008). The presence of neutrophilia in pre-therapy BAL was not only a positive predictor for subsequent response but also suggested a mechanistic role for azithromycin in this clinical setting (Gottlieb et al. 2008). The published reports on the benefits of ECP for BOS following HCT are even less compelling (Couriel et al. 2006; Lucid et al. 2011; Child et al. 1999), with only one focusing on patients with BOS post-HCT (Lucid et al. 2011). Stabilization in FEV1 was reported in six of nine patients in this retrospective report, comparing FEV1 values prior to and during ECP therapy (Lucid et al. 2011).

A phase II clinical trial using etanercept for the treatment of chronic lung injury post-HCT was reported in 2012 (Yanik et al. 2012). Etanercept was administered to 31 patients with either BOS ($n=22$) or restrictive lung disease ($n=9$), with NIH Consensus Criteria used to define the cohort of patients with BOS. For subjects with BOS, response was defined as a $\geq$10 % improvement in FEV1 within 4 weeks of therapy completion. Responses were noted in 7 of 22 (32 %) patients with BOS, with no differences in response based upon the severity of pulmonary disease at study onset. Therapy was well tolerated, with few infectious complications. Estimated 5-year OS was 90 % (95 % CI, 73–100 %) for patients who responded to therapy (Yanik et al. 2012). The study deserves particular notice for its use of strict eligibility and response criteria. All patients underwent pre- and post-therapy BAL, HRCT, plasma biomarker analysis, and PFTs, with additional PFTs performed monthly during therapy. No changes in adjuvant immune-suppressive therapy were allowed within the initial 28 days of therapy (Yanik et al. 2012).

The lack of defined response criteria greatly limits our ability to compare therapy strategies for BOS. Does a 10 % improvement in FEV1, as used in the etanercept BOS trial, even equate to improved performance? Are FEV1 and FEV1/FVC the best measures of airway obstruction (and response), or would changes in FEV1/slow vital capacity (SVC) serve as a better indicator of response in small airway disease (Au et al. 2011)? Should quality of life (QOL) assessments be included in the response analysis? The etanercept trial was unique in that validated quality of life (QOL) instruments were additionally used to assess patient performance during therapy. However, no difference in QOL outcome measures (pre-therapy vs. post-therapy) was noted in subjects that responded or did not respond to therapy (Yanik, unpublished observations).

The development of BOS likely involves an initial insult to lung parenchyma followed by an ongoing inflammatory process involving immune effector cells and the resident cells of the pulmonary vascular endothelium and interstitium. Much of our knowledge regarding the pathogenesis of BOS is based upon observations made in lung allograft recipients and from data generated in murine tracheal transplant models. Strong Th1 immune responses have been noted in rat heterotopic lung allografts, the Th1 response present even after fibrosis and airway obliteration was complete (Boehler et al. 1999). Several groups have shown enhanced expression of TNFα, IL-8, TGFβ, and IL-1β during lung allograft rejection (Belperio et al. 2002; Elssner et al. 2000; Fattal-German et al. 1998; El-Gamel et al. 1999) and additionally revealed critical roles for both RANTES and MCP-1 in the development of experimental BOS (Belperio et al. 2000, 2001). Ultimately, advances in the management of BOS will require improvements in our understanding of the basic pathophysiology of the disorder. A murine model for BOS has been reported, with peribronchiolar inflammation and airway resistance in the mice mimicking the human model (Panoskaltsis-Mortari et al. 2007; Srinivasan et al. 2012). The potential benefits of this murine model remain to be elucidated, in terms of improving our understanding of this enigmatic disorder and designing optimal treatment strategies.

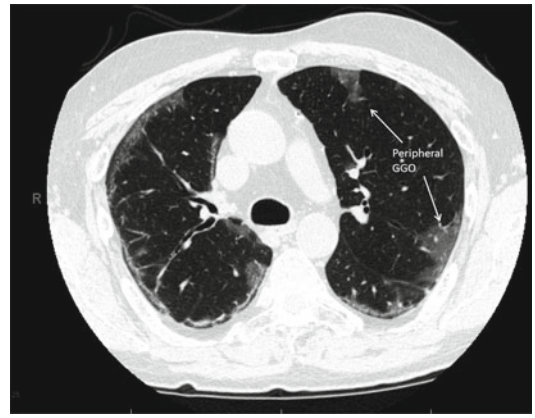


Fig. 5.3 Computed tomography of bronchiolitis obliterans organizing pneumonia (BOOP), with presence of peripheral ground-glass opacification (GGO, *arrows*). Reprinted with permission from Current opinions in oncology. 2013, Vol 25:187–194, Walters Kluwer Health. Lippincott Williams and Wilkins

5.2.4.5 Bronchiolitis Obliterans Organizing Pneumonia

Bronchiolitis obliterans organizing pneumonia (BOOP) was first described in allogeneic HCT in the early 1990s, presenting as acute bilateral airspace disease within the first 2–6 months post-transplant (Thirman et al. 1992; Mathew et al. 1994) (Fig. 5.3). In contrast to BOS, in which bronchiolar damage predominates, BOOP is primarily an alveolar disorder. The disorder is characterized by extensive infiltration of granulation tissue within alveoli, with fibroblasts and a matrix of loose connective tissue deposits. The pathophysiology is poorly understood, though a strong association with acute and/or chronic GVHD (Freudenberger et al. 2003; Jinta et al. 2007), a possible link to HLA B35 (Yotsumoto et al. 2007), and decreased incidence following T-cell-depleted HCT (Ditschkowski et al. 2007) are all supportive of an alloimmune mechanism. To avoid confusion with BOS, the disorder has been renamed cryptogenic organizing pneumonia (COP) in the pulmonary community.

Though consensus diagnostic criteria are lacking, the incidence of BOOP is estimated at 1–2 %, based upon single institution reports (Freudenberger et al. 2003; Jinta et al. 2007). In contrast to IPS and BOS, BOOP typically presents with fever, dyspnea, and a nonproductive cough, with PFTs revealing a restrictive defect (FVC <80 %, FEV1/FVC ≥80 %) (Table 5.3). HRCT reveals peripheral air space consolidation, with ground-glass and nodular opacities commonly identified (Lee et al. 1994; Pipavath et al. 2012). Given the clinical presentation and radiographic findings, infectious etiologies must be ruled out in all patients. Despite the collective support for the diagnosis of BOOP based upon clinical findings and radiographic presentation,

Table 5.3 Idiopathic pneumonia syndrome (IPS), bronchiolitis obliterans syndrome (BOS), and bronchiolitis obliterans organizing pneumonia (BOOP)

Characteristic	IPS	BOS	BOOP
Incidence	2–15 %	4–8 %	1–2 %
Clinical features	Dyspnea Cough	Dyspnea Cough Wheezing	Dyspnea Cough Fever
Risk factors	Full intensity regimen Acute GVHD	Chronic GVHD Hypogammaglobulinemia ↓ FEV1 pre-HCT	TBI regimen Active GVHD
Consensus criteria	Yes	Yes	No
PFTs	↓ TLC ↓ DLCO	FEV1 <75 % FEV1/FVC <0.7 RV >120 %, RV/TLC >120 %	FVC <80 % FEV1/FVC ≥70 % TLC <80 %, ↓ DLCO
Radiographic features	Diffuse infiltrates	CXR: Hyperinflation, normal	Consolidation
Computed tomography	Diffuse interstitial infiltrates	Air trapping, bronchiectasis, septal thickening	Peripheral ground-glass or nodular opacities
Treatment	Systemic corticosteroids TNF inhibitors	Systemic corticosteroids Inhaled corticosteroids Other immune suppressants	Corticosteroids

Adapted from Yanik and Kitko (2013)
GVHD graft-versus-host disease, *PFTs* pulmonary function testing, *TLC* total lung capacity, *DLCO* diffusion lung capacity for carbon monoxide, *FEV1* forced expiratory volume in 1 second, *FVC* forced vital capacity, *RV* residual volume, *CXR* chest radiograph, *HCT* hematopoietic cell transplant, *TBI* total body irradiation, *TNF* tumor necrosis factor

transbronchial or surgical lung biopsy approaches are still considered the gold standard for diagnosis (Alasaly et al. 1995; Wells 2001).

There is no standard treatment for BOOP, and no clinical trials are currently listed on *clinicaltrials.gov*. Based on limited retrospective reviews, systemic corticosteroids (1.0 mg/kg/day) would be considered the treatment of choice, with prolonged treatment courses recommended secondary to high rates of recurrence during taper (Thirman et al. 1992; Mathew et al. 1994; Freudenberger et al. 2003; Jinta et al. 2007). Reported response rates are 50–60 %, with overall survival approximately 50–70 % (Freudenberger et al. 2003; Jinta et al. 2007).

Our overall understanding of BOOP is limited, with no consensus diagnostic criteria, a lack of prospective trials and minimal understanding of the underlying pathophysiology. All three disorders IPS, BOS, and BOOP are postulated to be caused by alloimmune injury. However, why such alloreactivity would selectively target the interstitium and broncho-alveoli in IPS, bronchiolar structures in BOS, and the alveoli in BOOP remains poorly understood.

5.3 Hepatic Veno-occlusive Disease/Sinusoidal Obstruction Syndrome

5.3.1 Incidence of Veno-occlusive Disease/Sinusoidal Obstruction Syndrome

Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is a potentially life-threatening complication after HCT. Hepatic VOD/SOS affects both adult and pediatric populations and both allogeneic and autologous graft recipients, with a higher incidence in the allogeneic setting (Richardson et al. 2012; Carreras 2012). The onset of VOD/SOS is well described within the first 30 days after HCT

(Richardson et al. 2012), though later occurrences have been reported. It is characterized by clinical features including hepatomegaly, jaundice, weight gain, and ascites (Carreras et al. 2011; Coppell et al. 2010). VOD/SOS is reported to occur in 8–14 % of patients following HCT (Carreras et al. 2011), although incidence rates may be as high as 60 % in higher-risk patients (such as those with underlying liver disease and certain specific drug exposures, including gemtuzumab ozogamicin and sirolimus), and depending upon the diagnostic criteria used (Carreras et al. 2011; Coppell et al. 2010). Severe VOD/SOS is typically associated with multiorgan failure (MOF) and high mortality rates (>80 %) (Carreras et al. 2011; Coppell et al. 2010). Even among patients with moderate VOD/SOS, the mortality rate is still estimated at approximately 20 % (McDonald et al. 1984).

5.3.2 Pathogenesis of VOD/SOS

VOD/SOS is thought to be triggered by activation of and damage to the sinusoidal endothelial cells (SECs) in zone 3 of the hepatic acinus due to conditioning regimen-mediated injury (Guglielmelli et al. 2012). As shown in Figure 5.4, exposure of SEC's to conditioning radiation or toxic metabolites of chemotherapy leads to SEC injury and activation. Activated SECs express cytokines (e.g., TNFα and IL-1β) and adhesion molecules (e.g., ICAM-1 and VCAM-1) resulting in activation of proinflammatory pathways that further damage the endothelium (Coppell et al. 2003). This leads to the loss of endothelial wall fenestrae and formation of gaps between SECs (Panel B) (Carreras 2012). Consequently, red blood cells, leukocytes, and cellular debris extravasate into the space of Disse, causing progressive extraluminal compressive narrowing of the sinusoids (Carreras 2012; Coppell et al. 2003; Bearman 1995) and dissection of the endothelial cells, which could further embolize downstream and occlude the sinusoid (Panel C) (Carreras 2012). In addition, injury to the SECs of the sinusoids is also associated with a procoagulant and hypofibrinolytic state that contributes further to fibrin deposition, clot formation in situ, and narrowing of the sinusoids (Guglielmelli et al. 2012; Coppell et al. 2003; Bearman 1995). Together, these effects reduce hepatic venous outflow, leading to post-sinusoidal hypertension, central venular occlusion, hepatic enlargement with capsular distension, and, in more severe cases, portal venous flow reversal and hepatorenal syndrome, leading to multiorgan failure (MOF) and death (Carreras 2012) (Fig. 5.4).

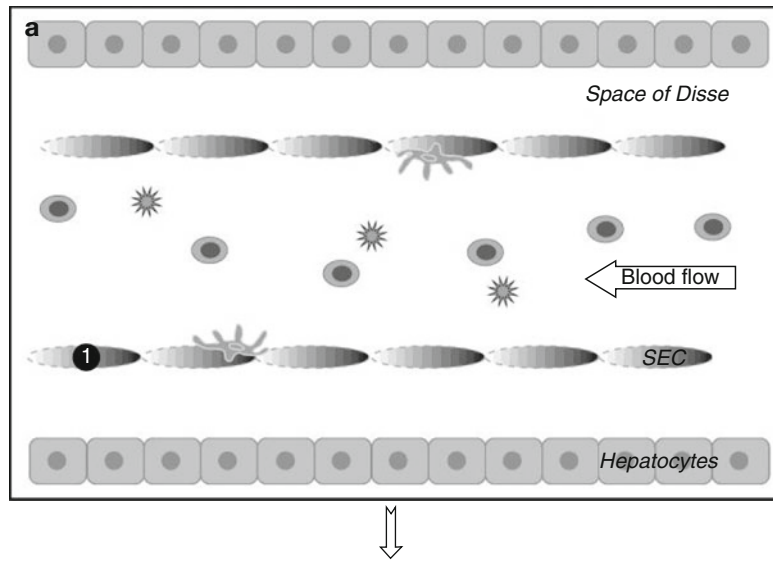
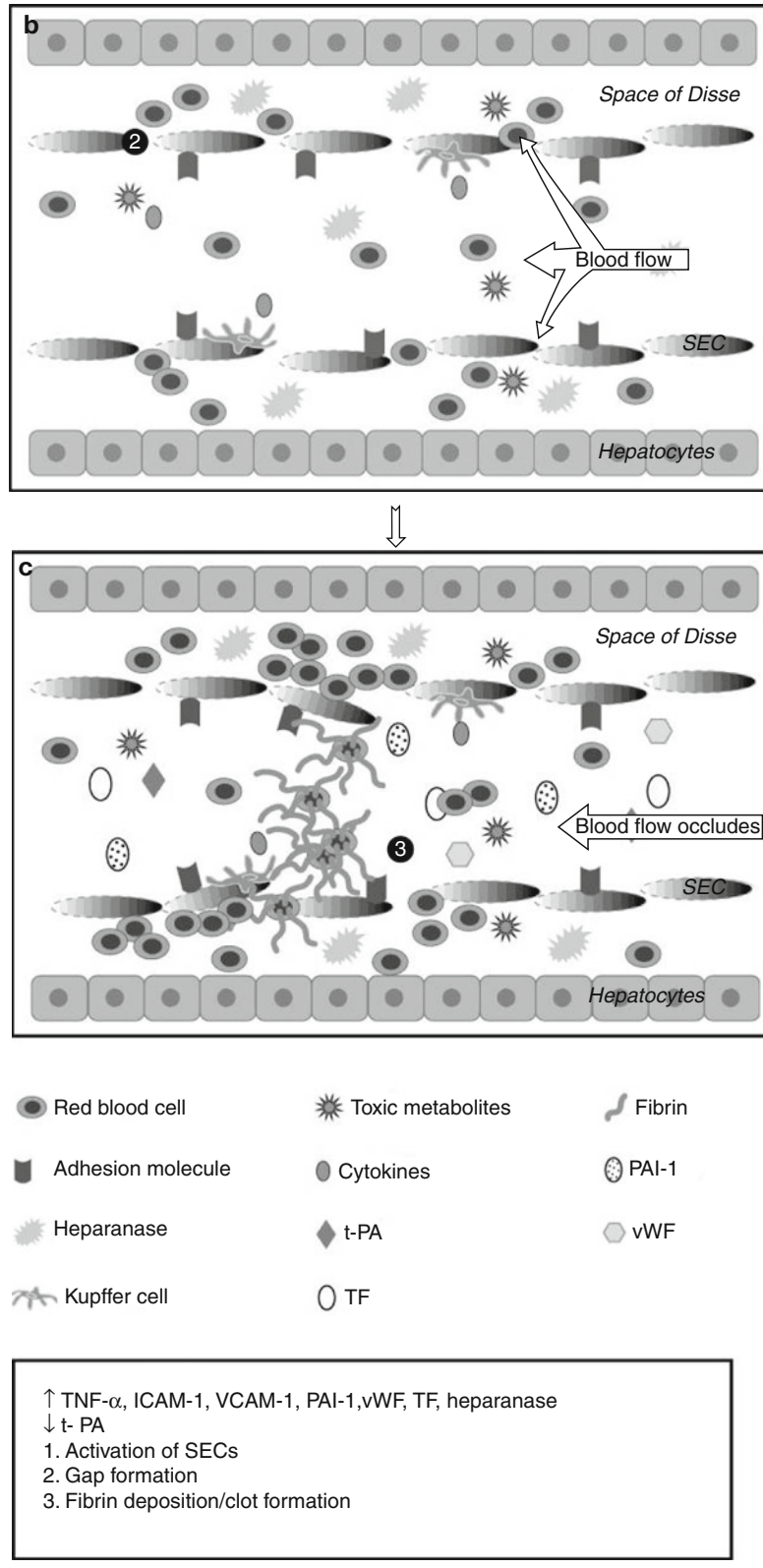


Fig. 5.4 Mechanisms of action of defibrotide (DF) (Adapted with permission from Richardson et al. (2013))

Fig. 5.4 (continued)



5.3.3 Diagnosis and Prognosis of VOD/SOS

The diagnosis of VOD/SOS is made based on clinical criteria with two established systems, the Seattle criteria (Bearman 1995) and the Baltimore criteria (Corbacioglu et al. 2012; Jones et al. 1987; Richardson et al. 1998). The Seattle criteria require at least two or more clinical features including jaundice, painful hepatomegaly or ascites, and/or unexplained weight gain within 30 days of transplantation (Bearman 1995; Corbacioglu et al. 2012). The Baltimore criteria specify an elevated bilirubin level of at least 2.0 mg/dL and two or more of the following characteristics: hepatomegaly, ascites, or at least 5 % weight gain by day +21 post-HCT, with the Baltimore criteria validated according to both histopathologic features as well as outcome (Bearman 1995; Jones et al. 1987).

VOD/SOS presents with a wide clinical spectrum and is conventionally divided into mild, moderate, and severe disease (McDonald et al. 1993). Mild VOD/SOS is considered disease that meets diagnostic criteria, does not require specific treatment for fluid excess or medication for hepatic pain, and has a self-limiting course. Moderate VOD/SOS reveals evidence of liver injury with need for active treatment for fluid excess or medication for hepatic pain but usually resolves completely. Severe VOD/SOS is defined in association with MOF and severe hyperbilirubinemia with rapid weight gain and has very high mortality rate (DeLeve et al. 2009). Although several biomarkers of endothelial injury have been described in the literature, including plasminogen activator inhibitor type-1 (PAI-1) (Nurnberger et al. 1998; Salat et al. 1994), no laboratory marker has been validated as a diagnostic marker of VOD/SOS. From retrospective analyses, the presence of multiorgan failure has emerged as the most useful marker for VOD/SOS severity to date. The Bearman model, developed in the 1990s, estimates the risk of developing severe VOD/SOS based on bilirubin level, percentage weight gain, and a designated time frame from HCT; this model has demonstrated some utility for predicting VOD/SOS severity. However, as the Bearman model was developed in a cohort of patients who developed VOD/SOS within 17 days of HCT after specific conditioning regimens, its general applicability to other conditioning regimens and later time frames post-HCT is limited (Carreras et al. 2011; Coppell et al. 2010; Bearman et al. 1993). In this context, sensitive and specific biomarker assays are needed that could guide disease prognostication and management, with some candidate markers under study but none yet defined.

5.3.4 Treatment Options and Patient Management for VOD/ SOS

Current management of VOD/SOS consists primarily of supportive care, with fluid management, adequate oxygenation, and transfusional support given to minimize ischemic liver injury, plus avoidance of known hepato-/nephrotoxins (DeLeve et al. 2009; Richardson et al. 2010). The use of tissue plasminogen activator with or without heparin has been evaluated in a number of studies. However, results have generally been disappointing. Approximately one-third of patients show response to thrombolytic therapy, although severe hemorrhages are common with therapy and can be life threatening with no survival advantage apparent (DeLeve et al. 2009) (Table 5.4).

Although there are no agents to date approved for the treatment of VOD/SOS either in the USA or Europe, the investigational drug defibrotide (DF) has shown the most promising results in clinical trials to date. DF has now been used in more than 1,800 patients worldwide and has demonstrated significant safety and tolerability, with low rates of drug-related hemorrhage (ref Gentium Announces Submission of a Marketing Authorization Application for Defibrotide to the European Medicines Agency, 2011). DF is a polydisperse oligonucleotide with fibrinolytic properties (but no significant systemic anticoagulation) and has shown protective effects on micro- and macrovascular endothelium. The use of DF for the

Table 5.4 t-PA with or without heparin for the treatment of VOD

Author	No. of patients	Dose (mg/day)	Duration (*d*)	Heparin (yes/no)	No. of responses	Life-threatening hemorrhage
Baglin et al. (1990)	1	50	4	No	1	0
Bearman et al. (1997)	42	5.4–120	2–4	Yes	12	10
Leahey et al. (1996)	9	5–10	2–4	Yes	5	0
Goldberg et al. (1996)	1	20	4	Yes	1	0
Higashigawa et al. (1995)	1	2–5	4	Yes[a]	1	0
Lee et al. (1996)	3	10–20	7–14	Yes	3	0
Yu et al. (1994)	3	0.25–0.5[b]	4	No	2	0
Schriber et al. (1999)	37	30–40	1–25	Yes	13[c] (2)[d]	13
Kulkarni et al. (1999)	17	10	1–12	Yes[e]	6	0

[a]Patient also received PGE
[b]Dose reported as mg/kg
[c]In patients who were suspected of VOD
[d]In patients who were diagnosed with VOD
[e]12 patients received heparin

Table 5.5 Prior clinical trials of defibrotide (DF) in the treatment of severe hepatic veno-occlusive disease (sVOD)/multiorgan failure (MOF)

Phase; pts	Condition	Design	Key end points	Other results
Phase I (Richardson et al. 1998) *N* = 19	sVOD post-HCT	Compassionate use: DF: 5–60 mg/kg/day (intra-pt dose escalation, until response/toxicity)	CR: 42 % No severe hemorrhage related to DF	Day +100 survival: 32 %
Phase I/II (Richardson et al. 2002) *N* = 88	sVOD post-HCT	Emergency use: DF: 5–60 mg/kg/day (intra-pt dose escalation, until response/toxicity)	CR: 36 %	Day +100 survival: 35 % No serious AEs attributed to DF
Phase II (Richardson et al. 2010) *N* = 149 (DF)	sVOD post-HCT	Randomized, dose-finding; Arm A: DF 25 mg/kg/day Arm B: DF 40 mg/kg/day For ≥14 days or CR, VOD progression or unacceptable toxicity	Overall CR: 46 % Effective dose 25 mg/kg/day	Day +100 survival: 42 % Treatment-related AEs incidence: 8 % (greater at 40 vs. 25 mg/kg/day)
Phase III (Richardson et al. 2009) *N* = 102 (DF) *N* = 32 (HC)	sVOD with MOF post-HCT	Nonrandomized, comparison to HC; DF: 6.25 mg/kg IV q6h (25 mg/kg/day) for ≥21 days	Day +100 CR DF 24 % HC 9 % ($p < 0.05$)	Day +100 mortality: DF 62 %; HC 75 % ($p = 0.051$) Hemorrhagic AEs: DF 65 %; HC 69 %

Designated an orphan drug by the FDA and EMA
Pt(*s*) patient(s), *HC* historical control, *q6h* every 6 hours, *CR* complete response, *IV* intravenous, *AEs* adverse events

treatment of VOD/SOS is supported by a number of large clinical trials showing that DF improves both complete response (CR) and survival, with a recent multicenter randomized phase II study establishing an effective DF dose of 25 mg/kg/day, given in divided doses intravenously every 6 hours (Richardson et al. 2010) (Table 5.5).

The efficacy of DF for the treatment of VOD/SOS was initially demonstrated in a retrospective study of 19 patients with VOD/SOS plus MOF, showing complete resolution of VOD/SOS in eight patients (42 %), six of whom survived for longer than 100 days with no significant bleeding observed (Richardson et al. 1998). A number of

trials have subsequently confirmed the efficacy of DF, with a European multicenter compassionate-use study demonstrating a 55 % CR rate in 40 treated patients (Chopra et al. 2000). A pivotal phase III trial of DF in 102 patients with VOD/SOS plus MOF showed a superior 100-day CR rate in the DF group when compared with historical controls treated without DF (24 % vs. 9 %, respectively; adjusted $p=0.015$) and a lower 100-day mortality rate (62 % vs. 75 %, respectively; adjusted $p=0.051$). In 2007, the FDA permitted access to DF in the USA through an investigational new drug (IND) expanded access treatment protocol for patients with VOD/SOS plus MOF. An analysis of 269 patients enrolled between December 2007 and March 2011 at 67 US centers on this compassionate-use study revealed a 32 % CR rate by day 100 post-HCT, with a day 100 overall survival of 50 % (Richardson et al. 2011).

The promising results observed with DF in VOD/SOS treatment trials have led to investigation of its use as prophylaxis for VOD/SOS following HCT. A number of prospective historically controlled trials have reported benefits with DF prophylaxis in pediatric patients at high risk of developing VOD/SOS (Cappelli et al. 2009; Corbacioglu et al. 2006; Qureshi et al. 2008). These studies are also supported by the recent prospective multicenter phase II/III study in Europe (Corbacioglu 2012). In this trial, 360 children (<18 years) who were undergoing myelo-ablative HCT were randomized to receive either prophylactic DF from conditioning to 30 days post-HCT or no prophylaxis (as a control group). In an intent-to-treat analysis, there was a 40 % reduction in VOD/SOS by day 30 post-HCT in patients receiving prophylactic DF when compared with control (12 % vs. 20 %; $p=0.051$). Of note, the mortality at 100 days was four times higher in patients who developed VOD/SOS compared to those without VOD/SOS (25 % vs. 6 %; $p<0.0001$). Interestingly enough, the incidence of acute GVHD was also significantly lower in the DF prophylaxis arm, an observation consistent with similar findings in treatment studies (Richardson et al. 2010).

5.3.5 Future Directions

Despite the promising results from clinical trials with DF as treatment and prevention of VOD/SOS, day 100 mortality from VOD/SOS remains unacceptably high. The importance of early intervention is key, with recent clinical observations indicating that delays in the initiation of VOD/SOS treatment are associated with worse outcomes (Richardson et al. 2011). The role of DF in VOD/SOS management may, in fact, be optimized with its use in early disease or as prophylaxis. Additional prospective studies in VOD/SOS prevention are now planned in adult HCT populations and specific high-risk settings. Elevations of von Willebrand factor, thrombomodulin, E-selectin, and soluble ICAM-1 before and early after allogeneic transplantation may be useful in predicting VOD/SOS in patients receiving sirolimus (Cutler et al. 2010) as GVHD prophylaxis and could lead to preemptive treatment or prevention trials based on these and other biomarkers (Richardson et al. 2012). Finally, additional therapies, such as low molecular weight heparin, N-acetyl cysteine, antithrombin III, and other novel antithrombotics may warrant further investigation in combination with DF (Richardson et al. 2012; Ho et al. 2008).

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