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Idiopathic pneumonia syndrome following hematopoietic stem cell transplantation

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Abstract. Non-infectious lung injury following hematopoietic stem cell transplant may be driven by either immune or non-immune pathways of inflammation. Common alloimmune lung complications include idiopathic pneumonia syndrome (IPS), transfusion related lung injury, diffuse alveolar hemorrhage, and peri-engraftment respiratory distress syndrome, with both diffuse alveolar hemorrhage and peri-engraftment respiratory distress syndrome existing as subsets of IPS when infection is absent. This review will discuss the definitions, risk factors, and pathogeneses of IPS and highlight the diagnostic work-up and novel approaches to treatment.

Keywords: Hematopoietic stem cell, idiopathic pneumonia syndrome, diffuse alveolar hemorrhage, respiratory distress syndrome

1. Introduction

Pulmonary dysfunction occurs frequently following hematopoietic stem cell transplantation (HSCT) and remains the major contributor to morbidity and mortality in transplant recipients [1–4]. Historically, one-half of all pulmonary complications after HSCT have been secondary to infection, and this remains a significant problem, particularly in patients with acute or chronic graft versus host disease (GVHD). Recently, the judicious use of broad-spectrum antimicrobial agents has tipped the balance toward non-infectious causes [5]. Non-infectious lung injury can be either acute or chronic depending upon the time of onset after HSCT and the tempo of disease progression. Although non-infectious lung injury can be observed in the autologous setting, the allogeneic response significantly enhances the severity of disease. This review will discuss the definitions, risk factors, and pathogeneses of idiopathic pneumonia syndrome (IPS), a frequently fatal form of acute, non-infectious lung dysfunction occurring after HSCT.

2. Definition, clinical course, and spectrum of disease

IPS is defined as widespread alveolar injury following HSCT that occurs in the absence of active lower respiratory tract infection or cardiogenic causes [4, 6]. Diagnostic criteria of IPS include signs and symptoms of pneumonia, non-lobar radiographic infiltrates, abnormal pulmonary function, and the absence of infectious organisms as determined by bronchoalveolar lavage (BAL) or lung biopsy (Table 1) [2, 4, 6]. This definition was recently expanded to classify

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Table 1
Definition of idiopathic pneumonia syndrome

Criteria
I-Evidence of widespread alveolar injury
Multi-lobar infiltrates on routine chest radiographs or computed tomography
Symptoms and signs of pneumonia (cough, dyspnea, tachypnea, rales)
Evidence of abnormal pulmonary physiology
Increased alveolar to arterial oxygen difference
New or increased restrictive pulmonary function test abnormality
II-Absence of active lower respiratory tract infection based upon
Broncho-alveolar lavage negative for significant bacterial pathogens including: acid-fast bacilli, Nocardia, and Legionella species
Broncho-alveolar lavage negative for pathogenic nonbacterial microorganisms
Routine culture for viruses and fungi
Shell vial culture for cytomegalovirus and respiratory syncytial virus
Cytology for cytomegalovirus inclusions, fungi, and *Pneumocystis jiroveci* (carinii)
Direct fluorescence staining with antibodies against cytomegalovirus, respiratory syncytial virus, herpes simplex virus, varicella zoster virus influenza, parainfluenza virus, adenovirus, and other organisms
Other organisms/tests to also consider
Polymerase chain reaction for human metapneumovirus, rhinovirus, coronavirus, and human herpesvirus 6
Polymerase chain reaction for Chlamydia, Mycoplasma, and Aspergillus species
Serum galactomannan enzyme-linked immunosorbent assay for Aspergillus species
Transbronchial biopsy if condition of the patient permits
III-Absence of cardiac dysfunction, acute renal failure or iatrogenic fluid overload as etiology for pulmonary symptomatology

IPS based on the primary anatomical sites of injury and dysfunction in an attempt to better characterize the clinical spectrum of disease and more carefully match subtypes of IPS with pre-clinical models that have been developed to study them [4]. A variety of histopathologic findings have been associated with IPS, and interstitial pneumonitis (a term historically used interchangeably with IPS) is the most frequently reported pattern [7]. The incidence of IPS in the first 120 days after allogeneic HSCT following high-dose conditioning ranges between 3% to 15%, depending upon the donor type (related versus unrelated), degree of antigenic mismatch, and conditioning regimen intensity [2–4, 6]. The median time of onset for IPS was historically reported to be 6 to 7 wk (ranging from 14 to 90 days) after HSCT [6], and mortality rates ranged from 50% to 80%, with more than 95% mortality in patients requiring mechanical ventilation [4]. A more recent retrospective study found a lower incidence and earlier onset of IPS than previously reported, but the clinical course involving the rapid onset of respiratory failure leading to death remained unchanged [3]. Long-term survival in pediatric patients with IPS is also quite poor [8].

The clinical spectrum of IPS encompasses several forms of pulmonary toxicity (Fig. 1). In a subset of patients, diffuse alveolar hemorrhage (DAH) may occur. DAH generally develops early post-HSCT, and is characterized by progressive shortness of breath, cough, and hypoxemia, with BAL fluid showing increasingly bloodier returns with sequential instillations of saline [9]. Mortality is high despite aggressive treatment with high-dose steroids, and death usually

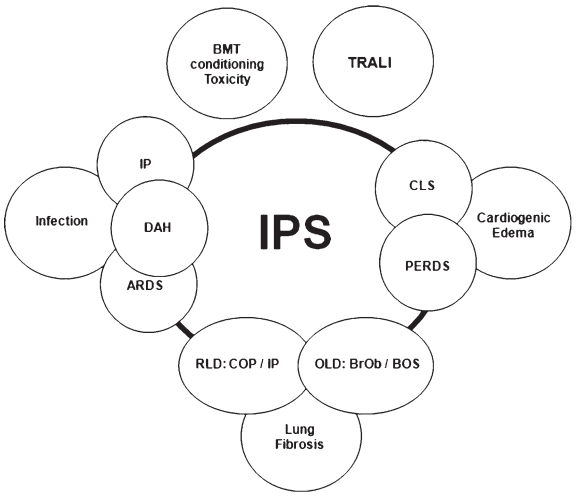

Fig. 1. Clinical spectrum of idiopathic pneumonia syndrome. The clinical spectrum of idiopathic pneumonia syndrome includes a variety of descriptive forms of lung injury that may share clinical features with toxicity incurred by chemo-radiotherapy, cardiogenic edema, pulmonary fibrosis, infection and transfusion associated lung injury. TRALI = Transfusion associated lung injury; ARDS = Acute respiratory distress syndrome; COP = Cryptogenic organizing pneumonia; IP = Interstitial pneumonitis; BO = Bronchiolitis obliterans; BOS = Bronchiolitis obliterans syndrome; CLS = Capillary leak syndrome; DAH = Diffuse alveolar hemorrhage; PERDS = Peri-engraftment respiratory distress syndrome; RLD = Restrictive lung disease; OLD = Obstructive lung disease.

occurs within weeks of diagnosis [9]. Some patients with DAH can have microorganisms isolated from blood, BAL fluid, or tracheal aspirate. Infectious and non-infectious DAH were found to be related but distinct entities with extremely poor outcomes following therapy with steroids [10]. Peri-engraftment respiratory distress syndrome (PERDS) also falls within the definition of IPS. PERDS is characterized by fever, dyspnea, and hypoxemia that occur within 5 to 7 days of neutrophil engraftment [11]. PERDS in the autologous setting responds promptly to corticosteroids and is associated with a favorable prognosis [11], whereas response to therapy and overall outcomes are poor after allogeneic HSCT [3, 4, 12, 13]. DAH, PERDS, and other forms of non-infectious lung dysfunction are discussed in additional detail in a separate review article published in pediatric critical care medicine.

Transfusion related acute lung injury (TRALI) may be mistaken for IPS. TRALI is the leading cause of mortality following infusions of plasma-containing blood products, and occurs following 1:1000 to 1:5000 transfusions [14, 15]. Except for albumin, all plasma-containing blood products (whole blood, packed red blood cells, fresh frozen plasma, platelets, cryoprecipitate, granulocytes, and stem cell products) have been linked to the development of TRALI. The diagnosis of TRALI should be considered when dyspnea and respiratory distress occur within hours after any blood product transfusion. Diffuse pulmonary infiltrates are observed on chest radiograph, which reflects edema from increased pulmonary vascular permeability. Associated mortality rates of 5–10% links TRALI to nearly one-half of all transfusion-related deaths. Treatment is supportive and discontinuation of the blood products and initiation of respiratory support results in recovery within 3 to 4 days in the majority of patients. It is important to note that TRALI results from capillary leakage and is not an issue with fluid overload; therefore, the use of forced diuresis should be instituted with caution to prevent hypovolemia. In over 70% of cases, antibodies directed against human leukocyte antigen class I or II epitopes on recipient hematopoietic cells are identified during the TRALI event. In rare cases, the antibody may be present in the recipient's plasma, directed against transfused donor leukocytes [16].

Risk factors for IPS include conditioning with high-dose total body irradiation, acute GVHD, older recipient age, high-risk disease status, initial diagnosis of malignancy other than leukemia, and in some reports, the use of methotrexate for GVHD prophylaxis [4, 8, 17]. In a recent meta-analysis, investigators found that lung irradiation dose, cyclophosphamide dose, and the addition of busulfan were associated with the development of interstitial pneumonitis [18]. The cumulative incidence of IPS within 120 days of HSCT following a very reduced intensity conditioning (RIC) regimen was found to be significantly lower than the incidence observed following conventional conditioning, despite greater patient age and a similar incidence of acute GVHD [19]. These findings suggest that the intensity of HSCT conditioning contributes to the development of IPS, consistent with data generated from pre-clinical models showing that the lung is sensitive to the combined effects of radiation and alloreactive T cells. A recent study suggests that more robust RIC regimens and stem cell source may likely impact the incidence and severity of disease as well [20].

Potential causes for IPS include direct toxic effects of HSCT conditioning regimens, occult pulmonary infections, and soluble and cellular inflammatory mediators that have been implicated in the development of other forms of lung injury and acute GVHD. Acute GVHD often precedes or coincides with IPS clinically [4, 21], and the consistent association between lung injury and GVHD in rodents supports a mechanistic link between the two entities [22–25]. However, considering the lung as a true target organ of acute GVHD remains a topic of considerable debate. Epithelial apoptosis, considered pathognomonic for GVHD in traditional target organs, is not consistently observed in allogeneic HSCT recipients with IPS [7, 26]. Rather, a histologic spectrum of "pulmonary GVHD" ranging from early diffuse alveolar injury to cicatricial, bronchiolitis obliterans has been described [7]. The heterogeneity of pulmonary histopathology is further complicated by the 1) non-specific changes that occur after mechanical ventilation, 2) limited frequency that lung biopsies are performed on HSCT recipients, and 3) quality and quantity of lung tissue collected. In an attempt to address these issues, investigators suggested categorizing the disease entities falling under the umbrella of IPS by the primary anatomic site of cellular damage: the interstitial tissue, vascular endothelium, or airway epithelium based upon clinical presentation and findings from correlative mouse models [4]. While some cases may remain unclassifiable, this approach would support investigation focused on specific pathways of tissue injury and

facilitate the development of new strategies tailored to distinct subtypes of disease [4].

3. Animal models of human disease

To better define the pathogenesis of IPS, several rodent systems have been developed (Table 2 and reviewed in Ref. 4). These pre-clinical models have been used to replicate various presentations of IPS and have consistently shown that the development of non-infectious lung injury correlates with the presence of systemic GVHD. For example, a model using a complete major histocompatibility complex (MHC) mismatched donor/recipient strain combination best reproduces early-onset IPS. In this system, pulmonary toxicity is caused by the influx of host monocytes and donor T cells into the lungs of lethally irradiated mice within the first 2 wk of HSCT [25]. More clinically relevant murine systems exist with haplo-identical, multiple minor histocompatibility complex antigens, or isolated MHC class I or class II loci mismatches. These systems model IPS that develops during the first 2 to 3 mo after HSCT, and are characterized by donor leukocyte infiltration into the lung [4]. Two primary, reproducible histologic patterns are observed: a dense mononuclear cell infiltrate around pulmonary vessels and bronchioles, and an acute pneumonitis involving the interstitial and alveolar spaces [23, 27, 28]. Alterations in pulmonary function confirm that the observed lung inflammation is physiologically relevant [23, 25, 29]. Despite the presence of endothelial damage, DAH is not regularly seen in pre-clinical IPS models except when mice with severe GVHD are challenged with lipopolysaccharide (LPS). In this scenario, hemorrhage is associated with large increases in the levels of BAL fluid neutrophils, tumor necrosis factor alpha (TNFα), and LPS [23, 27].

4. The pathogenesis of IPS

The pathophysiology of IPS is complex, and emerging data suggests that the lung is susceptible to two distinct but interrelated pathways of immune-mediated injury: a T cell axis and an inflammatory cytokine axis. These pathways involve components of the adaptive and the innate immune responses, synergistic interactions between lymphoid and myeloid cells, and the release of soluble inflammatory molecules, which orchestrate the recruitment of immune cells to the lung, and contribute to tissue damage and dysfunction (reviewed in Ref. 4).

The importance of lymphocytes to lung injury after experimental HSCT has been demonstrated by several groups [22–25, 30]. Donor T cells are critical to the early inflammatory lung injury that develops within the first week of HSCT across MHC antigens, and continue to contribute to lung injury at later time points in fully MHC matched (with minor antigen mismatch) HSCT [24, 25]. Donor cytotoxic lymphocytes expressing granzyme B are present in the lungs of mice after allogeneic HSCT, co-localizing with activated macrophages [25]. Evidence for alloantigen-specific killing by donor cytotoxic lymphocytes using both perforin and Fas/FasL pathways has also been identified in the lung as early as 2 wk after transplant [31]. While both FasL and TNFα mediated cytolytic pathways are utilized during the evolution of IPS caused by Th1 (CD4+) T cells, Tc1 (CD8+) T cells use TNFα exclusively [31].

Recent studies have challenged the role of Th1/Tc1 effectors in the development of IPS and paradoxically showed that pulmonary inflammation is accelerated when interferon gamma (IFNγ) signaling is blocked [32]. These results were later confirmed and extended to show that IFNγ negatively regulates the expansion

Table 2
Animal models of idiopathic pneumonia syndrome

Hematopoietic stem cell transplant donors	Hematopoietic stem cell transplant recipients	Mismatch	Conditioning
B10.BR	CBA	Multiple minor antigens	TBI: 1100 cGy
C57BL/6	B10.BR	Complete mismatch	TBI: 750 cGy ± Cy
C57BL/6	B6.C-H2^{bm1}/By	MHC class I	TBI: 675 cGy
C57BL/6	B6.C-H2^{bm12}/KhEg	MHC class II	TBI: 675 cGy
B6C3F1 hybrid	B6C3F1 hybrid	None (syngeneic)	Cy, cisplatin, BCNU
C57BL/6	B6D2F1 hybrid	Haplo-identical	TBI: 1100 to 1300 cGy
C57BL/6	B6.C-H2^{bm1}/By	MHC class I	TBI: 1100 cGy
LP/J	C57BL/6	Multiple minor antigens	TBI: 1300 cGy

TBI = Total body irradiation; cGy = Centi-gray; Cy = Cytoxan; MHC = Major histocompatibility complex; BCNU = Bis-chloroethylnitrosourea.

of Th17+CD4 + T cells in the lungs during IPS [33]. *In vitro* differentiated Th17 cells also mediate severe pulmonary pathology in a mouse GVHD model [34], and the role of Th17 cells and the down-stream production of interleukin-6 (IL-6) in lung inflammation is currently an area of intense study. These findings notwithstanding, robust lung inflammation has been reproducibly observed in several models when INFγ receptor: ligand interactions are completely intact (reviewed in Ref. 4), a scenario that is likely more applicable to the human disease state.

Evidence for cytokine activation during the development of IPS has been demonstrated in clinical studies, which have found increased pulmonary vascular permeability and increases in BAL fluid and serum levels of several cytokines (TNFα, sTNFR receptors I and II, IL-6) and chemokines (IL-8, monocyte chemoattractant protein-1, monokine induced by IFN-γ) that regulate leukocyte recruitment to sites of inflammation [1, 13]. A causal role for TNFα in the development of experimental IPS has been established using strategies that either neutralize its effects [27] or use TNFα deficient mice as HSCT donors [30]. Neutralization of TNFα prevents enhanced pulmonary inflammation at the time of LPS challenge, and reduces the severity of lung injury when implemented during the natural course of disease [27]. Studies using genetically altered mice have shown that IPS is dependent upon donor-derived TNFα. While TNFα from both donor accessory cells (macrophage/monocytes) and T cells contribute to lung injury, the T cell component predominates [30].

Recent plasma proteomic studies revealed striking similarities between inflammation engendered during IPS in humans and mice and underscored a significant contribution of the acute phase response (TNFα/IL-6) signaling pathway during disease progression [35]. Moreover, results identified a set of robust markers predictive of disease progression and response to therapy, suggesting that patients whose innate immune response is "hot-wired" to respond to the release of microbial products with high level secretion of TNFα may be more likely to be protected via strategies that neutralize this protein [35]. However, strategies that neutralize TNFα do not completely abrogate lung injury [27, 30, 36] in the experimental and clinical settings, suggesting that other inflammatory mechanisms, including the generation of IL-6 and both oxidative and nitrosative stress, contribute to the development of IPS (reviewed in Ref. 4).

Pulmonary surfactant is produced by alveolar type II cells and is composed of a mixture of lipids and at least four surfactant proteins (SPs). By reducing surface tension, surfactant decreases the work of breathing, allowing alveoli to remain open at end expiration, and keeping alveoli dry. Two of the SPs, SP-A and SP-D, also have major roles in host defense and in regulating immune responses in the lung [37]. Reduced production of and dysfunction of SPs contribute to the clinical picture of hypoxemia, progressive dyspnea, and pulmonary edema seen in clinical IPS. Mice lacking SP-A or SP-D exhibit exaggerated allogeneic T cell-dependent inflammation and lung injury, and intra-tracheal instillation of human SP-A attenuates the manifestations of IPS in this setting [38]. In humans, low pre-HSCT serum levels of SP-D have been found to represent a risk factor for the development of IPS [39], and may be a valuable biomarker in acute lung injury [40]. Despite its overwhelming therapeutic success in premature infants, results of surfactant replacement trials for pediatric acute lung injury, including patients after HSCT, have been variable [41, 42]. A phase III study is underway in pediatric HSCT recipients determine the efficacy of novel surfactant preparations that closely resembles natural surfactant.

5. Targets of inflammation and injury during IPS

Many recent investigations identified pulmonary endothelial and epithelial cells as targets for direct alloimmune-mediated damage. Endothelial cell (EC) damage can be induced by transfer of allogeneic lymphocytes to immune deficient mice [43] and has been implicated as a direct contributor to the development of several HSCT-associated complications [44]. Evidence for EC injury and leak as demonstrated by pulmonary edema, enhanced total protein levels in BAL fluid, and increased wet to dry lung weight ratios, is also observed after clinical and experimental IPS [13, 25]. In pre-clinical models, EC apoptosis coincides with the onset of pulmonary pathology, is associated with elevations in BAL fluid TNFα levels, and is accompanied by enhanced mRNA expression of adhesion molecules on ECs [45]. Neutralization of TNFα early after allogeneic HSCT significantly reduces EC apoptosis and lung injury observed in mice [45]. TNFα may therefore function as both an effector and facilitator of lung injury by both contributing directly to EC

injury and by regulating the chemokine milieu in the lung during the early stages of IPS [30].

Recent proteomic analysis has revealed possible mechanisms involved in EC damage during IPS. Angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2) are peptide ligands for the receptor Tie-2 on the surface of ECs. These two proteins regulate vascular integrity [44]: Ang-1 promotes vessel stability and Ang-2 promotes vascular permeability. Levels of Ang-2 are increased in patients with acute respiratory distress syndrome and steroid refractory GVHD [46–48], and plasma levels of Ang-2 are significantly elevated in IPS patients compared to concentrations present in the same patients prior to the onset of symptoms and compared to HSCT controls [49]. Importantly, plasma levels of Ang-2 returned to baseline in IPS patients who responded to TNFα neutralization therapy, but continued to rise in non-responders. Of particular interest, Ang-2 sensitizes ECs to TNFα and regulates TNFα-induced adhesion molecule expression [50]; these findings directly support pre-clinical data generated using murine IPS models [45].

Epithelial apoptosis has not been consistently observed in allogeneic HSCT recipients with lung injury. The unique aspects of epithelial anatomy in the lung may help explain this discrepancy. Since there is no stratification or layering of pulmonary epithelial cells (as in the skin or intestine), identification of epithelial cell apoptosis may be more challenging. Experimental studies have however provided evidence for alveolar type II epithelial injury occurring in the presence of cytotoxic T lymphocytes [25]. Moreover, the administration of keratinocyte growth factor, a stimulator of type II pneumocyte proliferation, accelerated the repair of damaged alveolar epithelial cells and led to decreased lung injury [51]. Finally, a new murine model of bronchiolitis obliterans following allogeneic HSCT revealed that MHC class II expressing bronchiolar epithelial cells are surrounded by cells expressing granzyme B prior to the occlusion of the airways [52].

6. The diagnostic and therapeutic approach to patients with IPS

The approach to HSCT patients with pulmonary dysfunction is complex as both pulmonary and non-pulmonary causes are possible. Because symptoms of respiratory distress can progress rapidly once established, the timely coordination of care is essential to optimizing outcomes (Fig. 2). A meticulous history and physical exam is paramount and will help dictate which diagnostic tests and possible consultations with experts in the fields of pulmonology, cardiology, nephrology, radiology, and critical care medicine may be necessary. Determination of the severity of respiratory dysfunction, including an assessment of supplemental oxygen requirement, overall fluid balance, renal function, and cardiac output, should be followed by radiographic imaging. An initial chest X-ray or computerized tomography scan may identify the presence of lobar, multi-lobar, or diffuse pulmonary infiltrates. While such findings may impact the decision-making process, they are non-diagnostic in and of themselves.

In the absence of obvious non-pulmonary causes, bronchoscopy with BAL should be considered in order to optimally distinguish between infectious and non-infectious causes. BAL samples should be sent for a variety of diagnostic tests to determine the presence of community-acquired and/or hospital-acquired opportunistic infections. Bacterial, fungal, and cytological stains, quantitative cultures, direct fluorescent antibody stains, and centrifugation (shell vial) cultures should be performed. Polymerase chain reaction assays may also be very useful, particularly when interpreted in the context of other supportive and correlative data. *Pneumocystis jiroveci* (carinii) pneumonia may be identified through a number of techniques, including cytological studies, special stains, or polymerase chain reaction-based assays. Despite a large number of published reports, the need to complete BAL in HSCT recipients with respiratory compromise remains a matter of debate, particularly in those patients who are critically ill. In two large series, the bronchoscopy related complication rates were less than 2% [53, 54] suggesting that the procedure can be completed safely in this scenario. The diagnostic yield from BAL fluid reportedly ranges from 31% to 67% depending on the time post-transplant respiratory distress occurs and the length of time between the onset of symptoms and the start of antibiotics until the procedure is performed [54–56]. However, since the medical management for non-infectious and infectious pulmonary dysfunction is quite different, making the appropriate diagnosis is important.

Once established, current standard treatment regimens for IPS (Table 3) include supportive care measures in conjunction with broad-spectrum antimicrobial agents and intravenous corticosteroids [4]. Unfortunately, outcomes for pediatric and adult

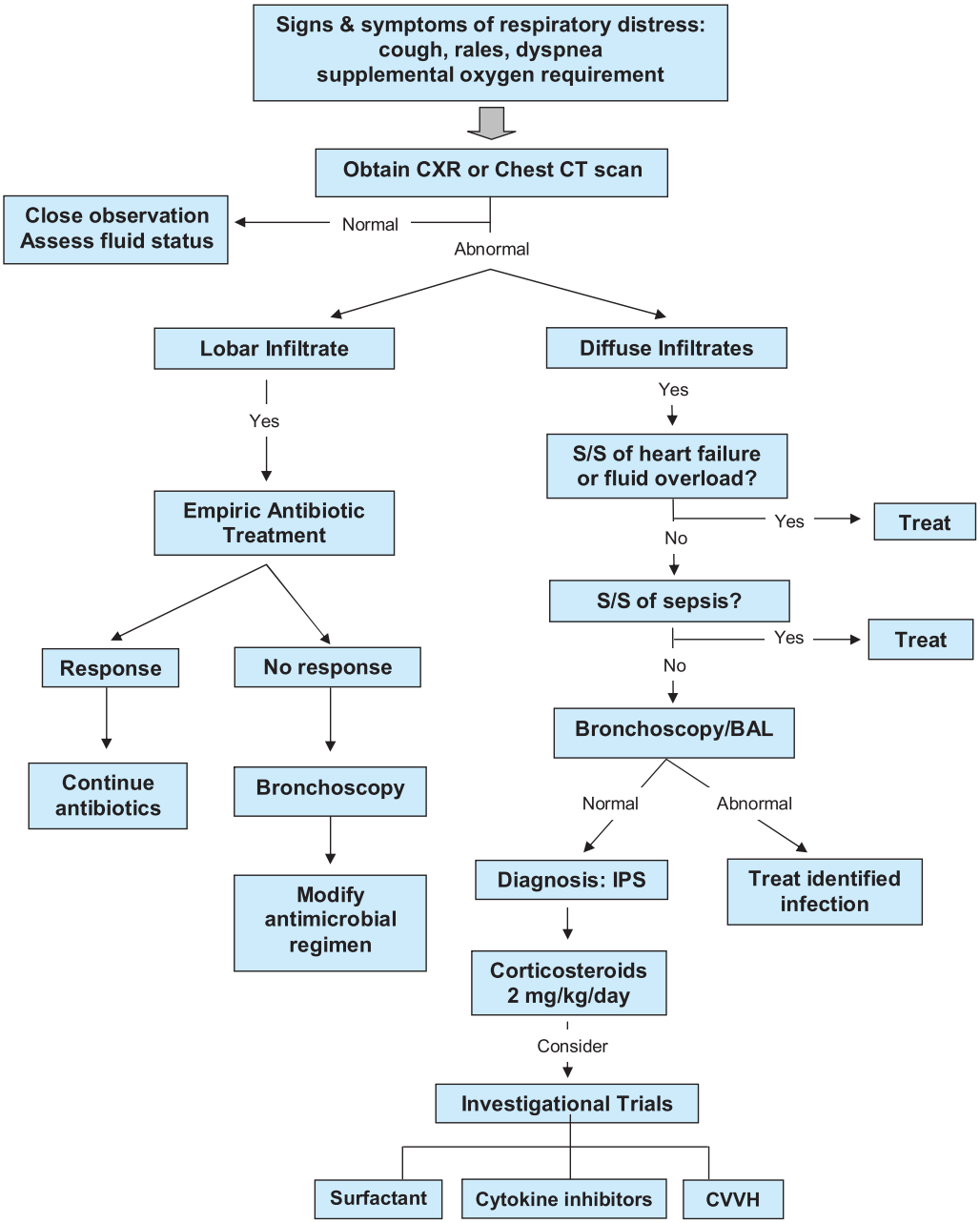

Fig. 2. Approach to hematopoietic stem cell transplantation patients with idiopathic pneumonia syndrome. The comprehensive approach to patients with idiopathic pneumonia syndrome is complex and includes completion of a thorough history and physical exam and the timely determination of the severity of respiratory dysfunction. An initial assessment of the need for supplemental oxygen support, overall fluid balance, renal function, and cardiac output should be followed by radiographic imagining. Results of the initial work-up will guide subsequent decision making toward initiation of empiric antimicrobial therapy versus consultation with medical and surgical specialists and consideration of bronchoscopy/ broncho-alveolar lavage to rule out infectious causes of lung inflammation. When pulmonary dysfunction is determined to be non-infectious in origin and immune suppressive therapy is considered, enrollment on open clinical trials is desirable whenever possible. CXR = Chest X-ray; CT = Computerized tomography; BAL = Broncho-alveolar lavage; IPS = Idiopathic pneumonia syndrome; CVVH = continuous veno-venous hemofiltration.

Table 3
Treatment options for idiopathic pneumonia syndrome

Supportive therapy
Supplemental oxygen, mechanical ventilation
Empiric broad spectrum antimicrobial agents pending culture results
Management of iatrogenic fluid overload
Continuous veno-venous hemofiltration
Immunosuppressive therapy
Corticosteroids (2 mg/kg/day)
Investigational: cytokine inhibitors, including anti-tumor necrosis factor agents

patients with IPS have been poor, underscoring the need for new therapeutic options. Response rates of 18 to 30% and mortality rates greater than 50% have been reported in patients treated with high-dose corticosteroids and supportive care measures. Three recent pediatric studies confirmed that IPS remains an important complication following HSCT in children, and mortality remains unacceptably high [8, 57, 58]. The early institution of continuous veno-venous hemofiltration may help to improve survival and oxygenation in some pediatric patients [59, 60]. Moreover, in a survey of North American pediatric HSCT centers, more than half of the centers report using renal replacement therapy prior to intubation in patients who develop respiratory distress [61]. However, prospective studies addressing the use of this treatment in this patient population are lacking.

As described above, translational research studies have suggested that neutralization of TNFα may be a useful option for IPS. In an early phase I/II study, etanercept, a TNFα binding protein, showed promise when given subcutaneously in combination with systemic steroids to patients with IPS [13]. Ten of 15 patients were able to completely withdraw from supplemental oxygen support and survival was significantly improved. Furthermore, in a retrospective study of patients treated with either corticosteroids alone or corticosteroids plus etanercept, overall survival was significantly higher in the etanercept treated group [62]. These encouraging results led to the development of two multi-institutional studies that were recently completed. An open label, phase II pediatric study revealed that the administration of systemic corticosteroids combined with etanercept resulted in response rates of 71% with day 28 survival of 89% and a 1 yr survival rate of 63%. Treatment responses were improved when children were treated prior to the development of severe lung dysfunction, at lower baseline fraction of inspired oxygen values, or prior to the requirement for mechanical ventilation [49].

The results of this trial warrant comparison with a parallel IPS study recently conducted in adults by the bone marrow transplant (BMT) clinical trials network (CTN) [20]. Both trials had uniform eligibility (excluding age), dosing schedules for both etanercept and corticosteroids, and response assessments. The BMT CTN trial was a randomized, phase III trial of corticosteroids along with etanercept or placebo. There were no significant differences in response or survival rates; response rates were 65% for the entire cohort, similar to the 71% response rate seen in the pediatric study. However, 1 yr overall survival was extremely poor (<25%) for adults in both arms compared to 63% observed in children, which superseded all previously published reports. Several other differences between the adult and pediatric trials are noteworthy, including the percentage of patients receiving RIC regimens (40% versus 4%), use of peripheral blood (~80% versus 11%) or cord blood (10% versus 39%) as the stem cell source. In addition, overall protocol adherence differed significantly between the two studies: 37% of patients on the etanercept arm in the adult study received ≤2 etanercept doses, whereas over 80% of patients in the pediatric IPS trial received all eight scheduled etanercept doses, irrespective of therapy response. Finally, interpretation of both studies is influenced by the number of patients enrolled. However, the pediatric trial terminated early when it successfully met an efficacy stopping rule, whereas the BMT CTN trial was terminated early due to poor accrual, with only 34 patients (out of a targeted 120) randomized [20]. Collectively, the completion of these trials suggests that conditioning intensity and stem cell source may influence the incidence and severity of IPS. Unfortunately, while the BMT CTN trial was drastically under-powered to draw any definitive conclusions, the likelihood of conducting a definitive phase III trial of etanercept in children with IPS is extremely low.

However, not all patients with IPS respond to etanercept therapy. A recent plasma proteomic study in patients with IPS provided a set of robust markers predictive for disease progression and response to therapy [35]. In addition, an effort to categorize patients with IPS based upon the presumed anatomic site of primary injury, in conjunction with mechanistic insights gained in the laboratory, may lead to the use of other promising, non-cross reactive therapeutic or preventive agents [4]. For example, it is conceivable that approaches to

maintain EC integrity may be effective at preventing or treating IPS. The administration of molecules that function as survival factors for ECs has been successful in preventing endothelial damage and mortality from septic shock and radiation injury. Similarly, ongoing studies examining the role of surfactant replacement therapy might prove useful in overcoming the effects of epithelial injury and dysfunction. Finally, since IPS develops and progresses to respiratory failure despite conventional immune suppression, it is possible that novel strategies directed toward inhibiting pathways of leukocyte recruitment to the lung may serve as future adjuncts to standard therapy. Such strategies have been successful in early phase studies for GVHD prevention [63].

In conclusions, lung injury remains a significant problem following allogeneic HSCT. Although lung injury occasionally occurs in the autologous setting, the allogeneic response significantly exacerbates the toxicity. A large preponderance of experimental data demonstrates that non-infectious disorders such as IPS have major immunologic components. Despite these findings, establishing the lung as a true target of GVHD remains a hotly debated topic. Inflammatory mediators such as TNFα and donor derived effector cells, which contribute to GVHD, are associated with IPS in the experimental and clinical settings. However, the absence of consistent evidence for epithelial apoptosis remains a major obstacle to considering the lung a target organ of acute GVHD. It is hoped that as animal models yield further insights, our understanding of this disease process will improve, ultimately leading to new therapeutic strategies to diagnose, treat, and prevent IPS in order to make HSCT a safer and more promising option for our patients. While mechanistic insights evolve, approaches combining current modalities including cytokine neutralization to reduce inflammation, targeted surfactant therapy to compensate for injured epithelium, and continuous veno-venous hemofiltration to optimize fluid balance during disease resolution may offer an intriguing opportunity for clinical trial development.

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