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Infectious Disease

Incidence, Risk Factors, and Outcomes of Idiopathic Pneumonia Syndrome after Allogeneic Hematopoietic Cell Transplantation

David S. Wenger1,*, Matthew Triplette1,2, Kristina Crothers1,3, Guang-Shing Cheng1,2, Joshua A. Hill4,5, Filippo Milano2,6, Shahida Shahrir1, Gary Schoch2, Lisa K. Vande Vusse1,2

1 Division of Pulmonary, Critical Care, and Sleep Medicine, University of Washington Medical Center, Seattle, Washington
2 VA Puget Sound Healthcare System, University of Washington, Seattle, Washington
3 Division of Allergy and Infectious Diseases, University of Washington, Seattle, Washington
4 Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington
5 Vaccine and Infectious Disease Division & Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington
6 Division of Hematology and Oncology, Seattle Cancer Care Alliance, Seattle, Washington

ABSTRACT

Our current knowledge of idiopathic pneumonia syndrome (IPS) predates improved specificity in the diagnosis of IPS and advances in hematopoietic cell transplantation (HCT) and critical care practices. In this study, we describe and update the incidence, risk factors, and outcomes of IPS. We performed a retrospective cohort study of all adults who underwent allogeneic HCT at the Fred Hutchinson Cancer Research Center between 2006 and 2013 (n = 1829). IPS was defined using the National Heart, Lung, and Blood Institute consensus definition: multilobar airspace opacities on chest imaging, absence of lower respiratory tract infection, and hypoxemia. We described IPS incidence and mortality within 120 and 365 days after HCT. We examined conditioning intensity (nonmyeloablative versus myeloablative with high-dose TBI versus myeloablative with low-dose TBI) as an IPS risk factor in a time-to-event analysis using Cox models, controlled for age at transplant, HLA matching, stem cell source, and updates in transplant outcomes[5].

INTRODUCTION

The term idiopathic pneumonia syndrome (IPS) is used to define a spectrum of noninfectious, diffuse lung injuries that occur following hematopoietic cell transplantation (HCT). Previous reports estimate that IPS develops in 4% to 12% of HCT recipients with a case fatality of 60% to 86% in the first 100 to 120 days post-transplant[1-4]. However, these estimates predate improvement in the diagnostic specificity of IPS, refinements in transplant practices, and advances in supportive critical care that have led to overall improvement in transplant outcomes[5].

IPS criteria include evidence of widespread alveolar injury with symptoms and signs of pneumonia in the absence of active lower respiratory tract infection[6]. Using updated molecular techniques for the detection of infectious pathogens in the lung, Seo et al.[7] have shown that over half of patients diagnosed with IPS have a virus detected in bronchoalveolar lavage (BAL) samples. The significance of these viruses in the pathogenicity of pneumonia remains unclear, but emerging evidence suggests that at least in the case of Human Herpesvirus 6 (HHV-6), these viruses may lead to lung injury and raise plausible concern that IPS may have been misdiagnosed in earlier studies[4,7,8].

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*Correspondence and reprint requests: David S. Wenger, MD, Division of Pulmonary, Critical Care, and Sleep Medicine, University of Washington Medical Center, 1999 NE Pacific Street, Seattle, WA 98109.
E-mail address: dswenger@uw.edu (D.S. Wenger).
IPS encompasses a spectrum of clinical presentations and is thought to result from a diversity of lung insults. Previously defined risk factors for the development of IPS after allogeneic HCT have included conditioning intensity, total body irradiation dose (TBI), high-grade acute graft-versus-host disease (GVHD), advanced age, and transplant indication. However, increased utilization of reduced-intensity conditioning regimens, improvements in prevention and treatment of acute GVHD, the introduction of umbilical cord blood stem cells, and improvements in the prevention and control of infectious complications have changed HCT-recipient exposures and may alter the spectrum of lung injury in patients who have undergone allogeneic HCT. We performed a retrospective cohort study in a contemporary cohort of patients who underwent allogeneic HCT. We rigorously adjudicated IPS status and herein report the updated incidence, risk factors, and outcomes of IPS. We hypothesized that conditioning regimen intensity and TBI dose would remain significant risk factors for the development of IPS and explored the risk of IPS relating to other recipient and transplant factors. Finally, given advances in supportive care practices, we hypothesized that mortality in patients who develop IPS would be lower compared with earlier studies.

PATIENTS, MATERIALS, AND METHODS

Study Patients

We performed a retrospective cohort study of all adults who underwent allogeneic HCT at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, Washington, between 2006 and 2013. We included only the first allogeneic HCT performed for each patient during this study period. Patients younger than 18 years and adults who received autologous grafts were excluded. The FHCRC Institutional Review Board approved this analysis.

Transplantation Techniques

All patients received a conditioning regimen followed by infusion of hematopoietic stem cell grafts according to local protocols. Although the conditioning regimens varied, the myeloablative conditioning regimens generally contained (1) busulfan with either cyclophosphamide or fludarabine, (2) treosulfan and fludarabine plus low-dose TBI (<12.0 Gray [Gy]), or (3) cyclophosphamide with or without fludarabine plus high-dose TBI (12.0 to 13.2 Gy) [10]. TBI dose fractionation schedules were tailored to the patient’s conditioning protocol. In general, our institution’s standard treatment protocol delivers 12-Gy total doses as twice-daily fractions of 2 Gy each over 3 consecutive days and 13.2-Gy total doses as twice-daily fractions of 1.65 Gy each over 4 consecutive days (dose rate, 6 to 25 Gy/min). Reduced-intensity nonmyeloablative regimens contained 2 to 4 Gy TBI with or without fludarabine. Most patients received immunosuppressive drugs, usually a calcineurin inhibitor and mycophenolate mofetil, for GVHD prophylaxis. Antimicrobial prophylaxis consisted of levofloxacin during neutropenia; (a)neutrophil count (ANC) ≤500 cells/mm³, acyclovir, trimethoprim-sulfamethoxazole, and fluconazole or a mold-active triazole. Preemptive therapy was used for cytomegalovirus (CMV) on the basis of weekly antigen or DNA testing [11]. For those with pulmonary symptoms, respiratory specimens were sent for microbiologic evaluation as described below. Acute GVHD was diagnosed clinically by the treating physician and graded according to previously described criteria [12].

Definition of IPS

IPS was defined using the National Heart, Lung, and Blood Institute consensus definition and required new multilobar airspace opacities on chest imaging, absence of lower respiratory tract infection, and abnormal pulmonary physiology [6]. By standard local practice, a broad panel of microbiologic studies was sent on all BAL samples. Any respiratory tract specimens obtained via BAL or lung biopsy, if performed, were submitted for cytologic and pathologic analyses with conventional staining and culture for bacteria, fungi, mycobacteria, nocardia, and viruses; shell viral centrifugation viral cultures for CMV and respiratory syncytial virus (RSV); and direct fluorescent antibody testing for Legionella, Pneumocystis jiroveci, CMV, RSV, parainfluenza virus types 1 to 3, and adenovirus. Serum and BAL were routinely tested for Aegyptis with the galactomannan index using the Bio-Rad Platelia Assay (Hercules, CA) [13]. In addition, a multiplex quantitative reverse-transcriptase PCR panel was used to detect 12 respiratory viruses, including influenza A, influenza B, RSV, parainfluenza virus types 1 to 4, adenovirus, human metapneumovirus, coronavirus, rhinovirus, and bocavirus [14]. Invasive fungal infections were defined according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria [15]. Bacterial pneumonia was diagnosed if the BAL culture grew 10³ to 40 colony-forming units per milliliter of pathogenic gram-positive cocci or if any number of gram-negative rods or other pathogens were isolated in the setting of compatible radiographic changes. Viral pneumonia was diagnosed if ≥40 PCR copies/μL of pneumonia-causing respiratory viruses were isolated. Because HHV-6 is a known human pathogen and may play a role in the pathogenesis of IPS [7], we retroactively tested remnants of clinical BAL samples available in local repositories for HHV-6 (n = 74). Participants with HHV-6 identified at ≥40 PCR/copies per microliter were censored on date of bronchoscopy (n = 9).

For all potential IPS cases meeting radiographic criteria with indeterminate BAL results, we performed a comprehensive manual chart review and considered factors such as response to medical therapies, relapses, serial BAL results, and autopsy results. IPS cases required sustained or progressive hypoxemia unresponsive to antibiotics or diuretics, defined as peripheral capillary oxygen saturation (SpO₂) <92%, an increase over baseline oxygen requirements to >1.0 liters per minute (LPM), or a new or increased-from-baseline A-a difference on arterial blood gases. IPS onset was defined as the day on which chest imaging first revealed multilobar infiltrates. Of note, each chest image and all potential IPS cases were reviewed by 2 experts and, in the event of disagreement, by a third to achieve consensus in the adjudication of this cohort (Supplementary Table S1).

Statistical Analyses

Patients with IPS were compared with patients without IPS using the Wilcoxon rank-sum test for continuous variables and Pearson’s chi-square test for categorical factors. Probability of IPS was estimated by cumulative incidence and incidence curve. We compared the cumulative incidence between predefined groups using Nelson-Aalen curves and log-rank tests.

We examined several potential IPS risk factors using bivariate Cox regression. Host factors of interest included patient age, sex, race/ethnicity, indication for transplant, recipient CMV serostatus, and lung function score (LFS; a combined measure of impairment in FEV₁ and DLCO). Additional transplant characteristics included hematopoietic stem cell source (cord blood versus peripheral blood or bone marrow), transplant type (HLA-matched related or unrelated or HLA-mismatched unrelated), and donor CMV serostatus. We used multivariable Cox regression models to examine the association between the primary exposure of interest, conditioning intensity, and development of IPS while controlling for potential confounders. Variables for the models were chosen a priori based on previous data on host factors and transplant characteristics associated with increased risk for IPS development [2,49]. IPS was a rare outcome in our cohort, and to avoid introducing bias by overfitting, we were parsimonious with variable inclusion [17]. We controlled for patient age at transplant, transplant type (HLA-matched versus unmatched), stem cell source (cord blood versus alternative source), and pretransplant LFS. Transplant type and stem cell source were dichotomized into hypothesized, clinically relevant categories, and LFS was modeled as a continuous variable.

Severe (grade III to IV) acute GVHD was not included in our final model because severe GVHD is more closely linked to myeloablative conditioning and may mediate the relationship between conditioning intensity and IPS [18-20]. In sensitivity analysis, we adjusted for severe acute GVHD occurring before IPS onset as a time-dependent covariate. Finally, race was added as a covariate in a separate sensitivity analysis. In our predominately white cohort, black/non-Hispanic race/ethnicity was collinear with HLA match and receipt of umbilical cord stem cells and therefore was not included in our primary model.

We examined associations between IPS and overall survival after HCT using Cox regression, modeling IPS as a time-dependent exposure. Bivariable Cox regression models were used to assess factors associated with post-IPS mortality at 120 days and 365 days after HCT. These factors were chosen based on associations with post-transplant respiratory failure or all-cause mortality [5,16]. We examined Schoenfeld residuals to assess proportional hazards assumptions of each time-to-event model and no violation was found. No adjustments were made for multiple comparisons; we considered 2-sided P values less than .05 to be statistically significant.

Analyses were performed using Stata version 15.0 (StataCorp LP, College Station, TX).

RESULTS

Cohort Characteristics and IPS Incidence

Our cohort consisted of 1829 adults who underwent allogeneic HCT at FHCRC between 2006 and 2013. BAL was performed in 332 patients who developed pulmonary infiltrates. Among these patients, pulmonary infections were identified in the specimens collected from 141 patients, which excluded these patients as possible IPS cases. After comprehensive chart review, 127 additional patients were excluded from the IPS group because of...
presumed cardiogenic pulmonary edema responsive to diuretics, rapid response to empiric antibiotics, or presence of extrapulmonary infectious source. Ultimately, 67 patients fulfilled IPS criteria. Median follow-up time was 485 days (range, 1 to 2836 days). The number of IPS cases was similar across calendar years throughout the study period (Supplementary Figure S1).

### Table 1
**Patient and Transplantation Characteristics**

| Factors                              | Patients without IPS (n = 1762) | Patients with IPS (n = 67) | P Value |
|--------------------------------------|---------------------------------|---------------------------|---------|
| Patient age, median (range), yr      | 49.7 (30.6-59.6)                | 51.9 (37.9-58.3)          | .47     |
| Female                               | 721 (40.9)                      | 29 (43.3)                 | .77     |
| Race                                 |                                 |                           | .003    |
| White                                | 1506 (85.5)                     | 53 (79.1)                 |         |
| Black                                | 27 (1.5)                        | 5 (7.5)                   |         |
| Asian                                | 101 (5.7)                       | 3 (4.5)                   |         |
| Alaska Native/Native American        | 128 (7.3)                       | 6 (8.9)                   |         |
| Ethnicity Latino                     | 98 (5.6)                        | 5 (7.5)                   |         |
| Allogeneic HCT prior to 2006         |                                 |                           | .70     |
| Yes                                  | 360 (20.4)                      | 15 (22.4)                 |         |
| No                                   | 1402 (79.6)                     | 52 (77.6)                 |         |
| Transplant indication                |                                 |                           | .85     |
| Acute leukemia                       | 848 (48.1)                      | 35 (53.0)                 |         |
| CML/MDS                              | 401 (22.7)                      | 13 (19.7)                 |         |
| Other malignancy                     | 445 (25.3)                      | 15 (22.7)                 |         |
| Lymphoma/CLL                         | 334 (75.1)                      | 12 (80.0)                 |         |
| Multiple myeloma                     | 110 (24.7)                      | 3 (20.0)                  |         |
| Other tumors*                        | 1 (0.2)                         | 0.0                       |         |
| Nonmalignant                         | 68 (3.9)                        | 3 (4.6)                   |         |
| Conditioning                          |                                 |                           |         |
| Nonmyeloablative                     | 765 (43.4)                      | 25 (37.3)                 | .01     |
| Myeloablative                        |                                 |                           |         |
| TBI ≤12 Gy                           | 688 (39.1)                      | 20 (29.9)                 |         |
| TBI >12 Gy                           | 309 (17.5)                      | 22 (32.8)                 |         |
| HLA and donor status                 |                                 |                           | .25     |
| Matched related                      | 579 (32.9)                      | 24 (35.8)                 |         |
| Matched unrelated                    | 718 (40.7)                      | 21 (31.4)                 |         |
| Mismatched unrelated                 | 308 (17.5)                      | 12 (17.9)                 |         |
| Stem cell source                     |                                 |                           | .09     |
| Peripheral blood                     | 1364 (77.4)                     | 42 (62.7)                 |         |
| Bone marrow                          | 241 (13.7)                      | 15 (22.4)                 |         |
| Cord blood                           | 157 (8.9)                       | 10 (14.9)                 |         |
| Disease risk*                        |                                 |                           | .31     |
| High                                 | 1634 (92.7)                     | 60 (89.6)                 |         |
| Low                                  | 128 (7.3)                       | 7 (10.4)                  |         |
| Recipient CMV serostatus             |                                 |                           | .11     |
| Positive                             | 1024 (58.9)                     | 46 (68.6)                 |         |
| Negative                             | 714 (41.1)                      | 21 (31.4)                 |         |
| Donor CMV serostatus                 |                                 |                           | .43     |
| Positive                             | 620 (38.6)                      | 19 (33.3)                 |         |
| Negative                             | 988 (61.4)                      | 38 (66.7)                 |         |
| Lung function score*                 |                                 |                           | <.001   |
| Normal (LFS = 2)                     | 637 (36.8)                      | 19 (29.2)                 |         |
| Mildly decreased (LFS 3-5)           | 979 (56.6)                      | 38 (58.5)                 |         |
| Moderately decreased (LFS 6-9)       | 110 (6.4)                       | 6 (9.2)                   |         |
| Severely decreased (LFS 10-12)       | 3 (0.2)                         | 2 (3.1)                   |         |

Values are presented as number (%) unless otherwise indicated.

CLL indicates chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HD, Hodgkin’s Disease; MDS, myelodysplastic syndrome; MM, multiple myeloma. Bolded P values represent statistically significant differences between those with and without IPS in the factors represented in column 1 corresponding to those P values. We defined P < 0.05 as statistically significant.

* High risk was defined as active, de novo, or relapsed acute myelogenous leukemia, MDS (refractory anemia with excess blasts or excess blasts in transformation), myeloproliferative disorder, acute lymphoblastic leukemia, CLL, non-Hodgkin lymphoma, HD, MM regardless of status, accelerated phase or blastic crisis of CML, or other tumors such as renal cell carcinoma. Low risk was defined as nonmalignant disease, including aplastic anemia, immunodeficiency syndrome, any of the diseases mentioned with unknown disease status or in remission except for MM, CML chronic phase, and MDS (refractory anemia with or without ringed sideroblasts).

1 Lung function score [16]. The pretransplant LFS represents the sum of the FEV1 and DLCO impairment scores, where >80% = 1, 70% to 79% = 2, 60% to 69% = 3, 50% to 59% = 4, 40% to 49% = 5, and <40% = 6.
Individuals who developed IPS were more likely to have received myeloablative conditioning that included high-dose TBI, have pretransplant lung function impairment, or be racially/ethnically black/non-Hispanic (Table 1). The cohort was predominantly white/non-Hispanic, and patients of black race were more likely to have received HLA-mismatched or umbilical cord stem cells and therefore more likely to have conditioning regimens that included high-dose TBI (25% versus 18%).

The cumulative incidence of IPS at 120 days after allogeneic HCT was 3.7% (incidence rate 3.1 cases per 10,000 person-days) (Figure 1). Among the 67 patients with IPS, 11 (16.4%) had acute GVHD before the onset of IPS, and 14 (20.9%) additional patients were diagnosed with GVHD following IPS diagnosis.

Risk Factors for IPS

In our primary analysis, myeloablative conditioning with high-dose TBI (≥12 Gy) was associated with increased risk of IPS in bivariate and fully adjusted models (adjusted hazard ratio [HR], 2.5; 95% confidence interval [CI], 1.2 to 5.2) (Table 2). No increased risk of IPS was observed in patients who received myeloablative conditioning with low-dose TBI compared with nonmyeloablative regimens. In fully adjusted Cox models, baseline lung impairment was associated with IPS development, whereas age and transplant indication, which have previously been identified as IPS risk factors, were not. Myeloablative conditioning with high-dose TBI remained associated with increased risk of IPS after further adjustment for severe acute GVHD (HR, 2.3; 95% CI, 1.1 to 4.8). In addition, adjustment for race/ethnicity did not change the magnitude of the association between conditioning intensity and IPS in fully adjusted models (HR, 2.6; 95% CI, 1.2 to 5.4).

Clinical Course and Outcome of IPS

Among the 67 patients who developed IPS, median time to IPS onset was 25 days after allogeneic HCT (range, 4 to 118 days). The median time between IPS onset and death was 43 days (range, 5 to 1894 days). Thirty-one patients (46.3%) with IPS died within the first 120 days of HCT and 47 patients (70.1%) died within 365 days of HCT. In contrast, among the 1762 patients who did not develop IPS in the first 120 days, unadjusted cumulative incidence curves stratified by conditioning regimen showed no significant difference in cumulative incidence of IPS between patients who received myeloablative versus nonmyeloablative conditioning (Figure 2). However, having received a myeloablative regimen with high-dose TBI (≥12 Gy) compared with receiving either myeloablative conditioning with low-dose TBI or nonmyeloablative conditioning was associated with an increased cumulative incidence of IPS.
204 (11.6%) died within 120 days of HCT and 510 (29.9%) died within 365 days of HCT. Among all transplant recipients who died within 365 days of HCT, 11.9% (47/557) died following a diagnosis of IPS. Finally, in the 265 patients who underwent bronchoscopy for pulmonary infiltrates and an alternative diagnosis to IPS was determined, 139 (52.4%) died with 365 days of HCT (Figure 3).

The development of IPS was associated with increased risk of death in the first 120 days following HCT at 2.1 (1.2-3.8) at 365 days (2.5 (1.2-5.2)).

### DISCUSSION

This study provided important updates in the incidence, risk factors, and outcomes of IPS. We demonstrated a lower incidence of IPS compared with historical reports (1-4,21), which may reflect advances in transplant practices or improved specificity in the diagnosis of IPS. We identified that myeloablative conditioning with high-dose TBI (≥12 Gy) remains an IPS risk factor and are the first to associate pre-transplant lung function impairment with risk for IPS development. We observed a lower mortality of patients with IPS 120 days after HCT compared with previous cohorts (1,2), but found that 1-year mortality remained high. This observation confirms that IPS continues to be associated with significant morbidity but that refinements in supportive care, advances in the prevention and care of immune-related toxicity, and/or improved classification of disease may be driving improvements in short-term survival.

TBI was previously identified as an IPS risk factor (22-24), but our study suggests that TBI dose may be the primary mediator of regimen-related pulmonary toxicity. Although myeloablative conditioning regimens that used high TBI doses were associated with IPS risk, myeloablative conditioning regimens with lower TBI doses were not. Experimental and observational studies support the role of TBI in IPS development. Murine models demonstrate that high-dose irradiation has multiple harmful effects in the lung. Radiation causes damage to lung endothelial DNA, resulting in cell death and acute lung injury, and simultaneously reduces tolerance to lung injury by promoting death of alveolar macrophage colony-forming cells, important mediators of pulmonary damage repair (25,26). In addition to total dose, several other radiation parameters have been identified as risk factors in the pathogenesis of pulmonary toxicity. There is general agreement that fractionated TBI is safer than single-dose TBI with respect to IPS (27); therefore, our center and others now use fractionated schedules. The role of the rate of delivering each TBI dose is debated (28); lower dose rates are generally preferred, and current American Society for Radiation Oncology guidelines recommend a dose rate of <0.2 Gy per minute (29,30). Finally, our center practices lung shielding, a technique to systematically reduce radiation exposure in the lung. The potential benefit from this practice is uncertain (31,32), and optimal protocols remain an area of active study.

Although this study was not specifically designed to examine pretransplant lung function, the novel finding of an association between baseline lung dysfunction and IPS is noteworthy. Pretransplant pulmonary function tests aid in the prognostication and identification of individuals at greater risk for post-transplant complications and mortality (16). Previous studies have linked impairments in DLCO and FEV1 to increased risk of post-transplant respiratory failure and all-cause mortality. Together with these prior studies, our finding warrants additional attention in future investigations and justifies continued caution in transplanting patients with severely reduced lung function.

**Table 2** Multiple Cox Regression Analysis of Idiopathic Pneumonia Syndrome Risk Factors

| Variable                      | Unadjusted Hazard Ratio (95% CI) | Adjusted Hazard Ratio (95% CI)* |
|-------------------------------|----------------------------------|---------------------------------|
| Conditioning regimen          | Reference                        | Reference                       |
| Nonmyeloablative              | Reference                        | Reference                       |
| Myeloablative with TBI <12 Gy | 0.9 (0.5-1.6)                   | 1.1 (0.6-2.0)                   |
| Myeloablative with TBI ≥12 Gy | 2.1 (1.2-3.8)                   | 2.5 (1.2-5.2)                   |
| Patient age                   | 0.9 (0.8-1.1)                   | 1.0 (0.8-1.3)                   |
| HLA and donor status          | Reference                        | Reference                       |
| Mismatched                    | 1.4 (1.0-2.0)                   | 1.2 (0.7-2.1)                   |
| Stem cell source              | Reference                        | Reference                       |
| PBSC or BM                    | 1.7 (0.9-3.4)                   | 0.9 (0.3-2.8)                   |
| Lung function score¹          | Per 1-point increase in impairment | 1.2 (1.1-1.4)                 |
| Acute GVHD                    | Reference                        | Reference                       |
| Grades 0-II                   | Reference                        | Reference                       |
| Grades III-IV                 | 3.6 (1.8-7.1)                  |                                 |
| Race/ethnicity¹               | White                            | Reference                       |
| Black                         | 4.7 (1.9-11.8)                  |                                 |
| Asian                         | 0.9 (0.3-2.7)                   |                                 |
| Alaska Native/Native American | 1.3 (0.6-3.1)                  |                                 |
| Transplant indication         | Reference                        |                                 |
| Nonmalignant                  | Acute leukemia                   | 1.0 (0.3-3.1)                  |
| CML/MDS                       | 0.7 (0.2-2.6)                   |                                 |
| Other malignancy              | 0.8 (0.2-2.7)                   |                                 |
| Recipient CMV serostatus      | Negative                         | Reference                       |
| Positive                      | 1.5 (0.9-2.5)                   |                                 |
| Donor CMV serostatus          | Negative                         | Reference                       |
| Positive                      | 0.8 (0.5-1.4)                   |                                 |

PBSC indicates peripheral blood stem cell; BM, bone marrow.

* Adjusted model controlled for conditioning regimen (primary exposure), age, type of transplant, stem cell source, and lung function score.

¹ Lung function score [16]. The pretreatment LFS represents the sum of the FEV1 and DLCO impairment scores, where > 80% = 1, 70% to 79% = 2, 60% to 69% = 3, 50% to 59% = 4, 40% to 49% = 5, and <40% = 6.

² Adjusted for in this analysis.
Moreover, it is hypothesized that lipopolysaccharide dysregulation promotes expansion of alloreactive T cells and injury [9,18,34-36]. In models of acute GVHD, similar experimental IPS models, TNF-α and IFN-γ mediate signal transduction cascades that orchestrate noninfectious lung inflammation and injury [9,18,34-36]. In models of acute GVHD, similar cytokine dysregulation promotes expansion of alloreactive donor CD4+ cells [19]. Moreover, it is hypothesized that lipopolysaccharide translocation from intestinal damage resulting from conditioning toxicity or acute GVHD may result in the neutrophilic alveolitis observed in the later stages of experimental IPS [9,37]. Although we agree that immune-mediated lung injury contributes to the development of IPS, our study suggests that GVHD does not account for the totality of risk, and additional factors must be involved in the pathogenesis of early noninfectious lung injury.

Historically, clinical outcomes among patients with IPS after conventional HCT have been uniformly poor. Zhu et al. [4] most recently described an 87% (20/23 patients) 1-year mortality in patients who developed IPS within 120 days of HCT (study cohort 1997 to 2007) using similar diagnostic criteria. In the analysis by Zhu et al. [4], median time to death following diagnosis was just 9 days (range, 3 to 92 days) compared with 43 days in our cohort. Although this may be influenced by longer follow-up in our study, we believe this provides evidence that recent improvements in supportive care along with advances in transplant practices may be responsible for improved short-term mortality. Treatment decisions were at the discretion of the provider, and assessing efficacy of novel treatment strategies was not the aim of this study. However, it should be noted that patients diagnosed with IPS typically received high-dose systemic steroids (2 to 4 mg/kg) and, in select cases of refractory disease, received the addition of etanercept, a soluble TNF-α-binding protein (0.4 mg/kg given twice weekly for a maximum of 8 doses) [38-40]. Despite improvements in short-term outcomes, 1-year mortality remains high. Firm conclusions cannot be drawn about this observation, but we speculate that profound morbidity resulting from IPS drives poor long-term recovery, and our data confirm that short-term survivors of IPS remain a high-risk group of allogeneic HCT recipients. Finally, the associations we found between the need for mechanical ventilation or other organ injury with poor IPS outcomes are consistent with results reported in larger series of HCT recipients [41,42]. Organ injury likely reflects overall illness severity and not necessarily a distinct pathologic entity, but these observations are important and may aid physicians as they counsel patients and families regarding prognosis.

This study had several limitations. Our single-center, predominantly white sample may limit generalizability, but the single-center design allowed for uniformity in practice patterns that may have improved our ability to assess for novel risk factors. The small number of cases restricted our ability to adjust completely for differences between patients with and without IPS, and it is possible that residual confounding exists; however, our very large cohort of well-characterized allogeneic HCT recipients allowed us to make several clinically relevant observations. Despite rigorous adjudication of cases, misclassification of IPS remains possible. We applied modern molecular techniques to identify previously occult viral pathogens, including HHV-6, but the possibility remains that we overestimated the incidence of IPS. Conversely, some patients with IPS might have been missed because of mild illness or because the patient was too ill to undergo an invasive diagnostic procedure. For these reasons, the incidence of IPS might have been underestimated.

The current study suggests that although the incidence and case-fatality of IPS may be declining, it remains significantly linked with post-transplant morbidity. Future study should focus on improved classification and early detection. Elucidating the pathogenicity of previously occult viral organisms to determine better the balance between infectious and noninfectious HCT pulmonary complications is critical. Study of serum biomarkers to diagnose IPS noninvasively at an earlier stage in disease development has shown promise and would have significant treatment implications but awaits prospective validation [43]. Finally, understanding the pathologic mediators of IPS (and its unique phenotypes) is essential to the discovery of novel treatment modalities and necessary to further improve long-term outcomes.

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Table 3
Mortality following IPS Onset

| Variable                                      | Total Number of Patients | No. (%) Patients Who Died within 120 Days of HCT | HR (95% CI) for Death after IPS and within 120 Days of HCT from Bivariable Cox Regression | No. (%) Patients Who Died within 365 Days of HCT | HR (95% CI) for Death after IPS and within 365 Days of HCT from Bivariable Cox Regression |
|-----------------------------------------------|--------------------------|--------------------------------------------------|------------------------------------------------------------------------------------------|-------------------------------------------------|-----------------------------------------------------------------------------------------|
| Mechanical ventilation*                       |                          |                                                  |                                                                                         |                                                 |                                                                                         |
| Not initiated                                 | 28                       | 8 (35)                                           | Reference                                                                                | 16 (57)                                         | Reference                                                                                |
| Initiated                                     | 39                       | 23 (59)                                          | 3.0 (1.3-6.6)                                                                            | 31 (79)                                         | 2.3 (1.3-4.3)                                                                            |
| Renal injury†                                 |                          |                                                  |                                                                                         |                                                 |                                                                                         |
| Creatinine <2 mg/dL                          | 51                       | 19 (37)                                          | Reference                                                                                | 32 (63)                                         | Reference                                                                                |
| Creatinine ≥2 mg/dL                          | 16                       | 12 (75)                                          | 2.7 (1.3-5.6)                                                                            | 15 (94)                                         | 3.1 (1.7-6.0)                                                                            |
| Hepatic injury†                               |                          |                                                  |                                                                                         |                                                 |                                                                                         |
| Total bilirubin <4 mg/dL                     | 52                       | 18 (35)                                          | Reference                                                                                | 32 (62)                                         | Reference                                                                                |
| Total bilirubin ≥4 mg/dL                     | 15                       | 12 (80)                                          | 3.8 (1.8-7.9)                                                                            | 14 (93)                                         | 2.4 (1.3-4.5)                                                                            |
| Severe acute GVHD (before IPS)               |                          |                                                  |                                                                                         |                                                 |                                                                                         |
| No or mild acute GVHD                        | 56                       | 25 (45)                                          | Reference                                                                                | 40 (71)                                         | Reference                                                                                |
| Severe acute GVHD (grade III or IV)          | 11                       | 6 (55)                                           | 1.3 (0.5-3.2)                                                                            | 7 (64)                                          | 1.6 (0.8-3.2)                                                                            |
| Conditioning intensity                        |                          |                                                  |                                                                                         |                                                 |                                                                                         |
| Nonmyeloablative                             | 25                       | 12 (48)                                          | Reference                                                                                | 20 (80)                                         | Reference                                                                                |
| Myeloablative TBI <12 Gy                     | 20                       | 10 (50)                                          | 1.0 (0.4-2.3)                                                                            | 16 (80)                                         | 1.0 (0.5-1.9)                                                                            |
| Myeloablative TBI ≥12 Gy                     | 22                       | 9 (41)                                           | 0.7 (0.3-1.7)                                                                            | 11 (50)                                         | 0.5 (0.3-1.0)                                                                            |
| Lung function score                          |                          |                                                  |                                                                                         |                                                 |                                                                                         |
| Normal (LFS = 2)                             | 19                       | 9 (47)                                           | Reference                                                                                | 14 (74)                                         | Reference                                                                                |
| Mildly decreased (LFS 3-5)                   | 38                       | 16 (42)                                          | 0.9 (0.4-2.0)                                                                            | 24 (63)                                         | 0.8 (0.4-1.6)                                                                            |
| Moderately decreased (LFS 6-9)               | 6                        | 2 (33)                                           | 0.6 (0.1-3.0)                                                                            | 5 (83)                                          | 1.2 (0.4-3.3)                                                                            |
| Severely decreased (LFS 10-12)               | 2                        | 2 (100)                                          | 8.9 (1.7-46.9)                                                                           | 2 (100)                                         | 9.2 (1.8-46.6)                                                                           |

* Ventilator support within 7 days of IPS diagnosis.
† Serum creatinine concentration >2 mg/dL within 3 days of IPS onset.
‡ Total bilirubin concentration >4 mg/dL within 3 days of IPS onset.

**SUPPLEMENTARY MATERIALS**

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jbbmt.2019.09.034.

**REFERENCES**

1. Afessa B, Litzow MR, Tefferi A. Bronchiolitis obliterans and other late onset non-infectious pulmonary complications in hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2001;28(5):425-434.
2. Fukuda T, Hackman RC, Guthrie KA, et al. Risks and outcomes of idiopathic pneumonia syndrome after nonmyeloablative and conventional conditioning regimens for allogeneic hematopoietic stem cell transplantation. *Blood*. 2003;102(8):2777-2785.
3. Sakaguchi H, Takahashi Y, Watanabe N, et al. Incidence, clinical features, and risk factors of idiopathic pneumonia syndrome following hematopoietic stem cell transplantation in children. *Pediatr Blood Cancer*. 2012;58(5):780-784.
4. Zhu K-E, Hu J-Y, Zhang T, Chen J, Zhong J, Lu Y-H. Incidence, risks, and outcome of idiopathic pneumonia syndrome early after allogeneic hematopoietic stem cell transplantation. *Eur J Haematol*. 2008;81(6):461-466.
5. Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. *N Engl J Med*. 2010;363(22):2091-2101.
6. Panoskaltsis-Mortari A, Grie G, Madtes DK, et al. An official American Thoracic Society research statement: noninfectious lung injury after hematopoietic stem cell transplantation: idiopathic pneumonia syndrome. *J Clin Invest*. 2011;116(9):1262-1270.
7. Seo S, Renaud C, Kuypers JM, et al. Incidence, clinical features, and risk factors of idiopathic pneumonia syndrome after hematopoietic cell transplantation. *Blood*. 2015;125(24):3789-3797.
8. Zhou X, O'Dwyer DN, Xia M, et al. First onset herpesviral infection and lung injury in allogeneic hematopoietic cell transplantation. *Am J Respir Crit Care Med*. 2019;200(1):63-74.
9. Cooke KR, Yanik G. Acute lung injury after allogeneic stem cell transplantation: is the lung a target of acute graft-versus-host disease? *Bone Marrow Transplant*. 2004;34:420-420.
10. Appelbaum FR. Optimising the conditioning regimen for acute myeloid leukaemia. *Best Pract Res Clin Haematol*. 2009;22(4):543-550.
11. Rautu T, Eriksson B, Remes K, et al. Ursodeoxycholic acid for the prevention of hepatic complications in allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2009;44(5):578-584.
12. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus conference on acute GVHD grading. *Bone Marrow Transplant*. 1995;15(6):825-828.
13. Fisher CE, Stevens AM, Leisenring W, Pergam SA, Boeckh M, Hohl TM. The serum galactomannan index predicts mortality in hematopoietic stem cell...
transplant recipients with invasive aspergillosis. Clin Infect Dis. 2013;57(7):1001–1004.

14. Waghmare A, Xie H, Kimball L, et al. Supplemental oxygen-free days in hematopoietic cell transplant recipients with respiratory syncytial virus. J Infect Dis. 2017;216(10):1235–1244.

15. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis. 2008;46(12):1813–1821.

16. Parrimont M, Madtes DK, Au DH, Clark JC, Chien JW. Pretransplant lung function, respiratory failure, and mortality after stem cell transplantation. Am J Respir Crit Care Med. 2005;172(3):384–390.

17. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis: II. Accuracy and precision of regression estimates. J Clin Epidemiol. 1995;48(12):1503–1510.

18. Mauermann N, Burian J, Gartner SR, et al. Interferon-γ regulates idiopathic pneumonia syndrome, a Th17+CD4+ T-cell–mediated graft-versus-host disease. Am J Respir Crit Care Med. 2008;178(4):379–388.

19. Varelas A, Gartlan KH, Krejviel E, et al. Lung parenchyma-derived IL-6 promotes IL-17A–dependent acute lung injury after allogeneic stem cell transplantation. Blood. 2015;125(15):2435–2444.

20. Carlson MJ, West ML, Coghill JM, Panoskaltsis-Mortari A, Blazar BR, Seryod JS. In vitro–differentiated TH17 cells mediate lethal acute graft-versus-host disease with severe cutaneous and pulmonary pathologic manifestations. Blood. 2009;113(6):1365–1374.

21. Keates-Baleeiro J, Moore P, Koyama T, Manes B, Calder C, Frangoul H. Incidence and outcome of idiopathic pneumonia syndrome in pediatric stem cell transplant recipients. Bone Marrow Transplant. 2006;38:285.

22. Girinsky T, Benhamou E, Bourhis JH, et al. Prospective randomized comparison of single-dose versus hyperfractionated total-body irradiation in patients with hematologic malignancies. J Clin Oncol. 2000;18(5):981–986.

23. Sorror M, Storer B, Sandmaier BM, et al. Hematopoietic cell transplantation-comorbidity index and Karnofsky performance status are independent predictors of morbidity and mortality after allogeneic nonmyeloablative hematopoietic cell transplantation. Cancer. 2008;112(9):1992–2001.

24. Volpe AD, Ferrari AJMA, Annaloro C, et al. Lethal pulmonary complications significantly correlate with individually assessed mean lung dose in patients with hematologic malignancies treated with total body irradiation. Int J Radiat Oncol Biol Phys. 2002;52(2):483–488.

25. Down JD, Easton DF, Steel GC. Repair in the mouse lung during low dose-rate irradiation. Radiother Oncol. 1986;16(1):29–42.

26. Lin H-S, Hsu S. Effects of dose rate and dose fractionation of irradiation on pulmonary alveolar macrophage colony-forming cells. Radiat Res. 1985;103(2):260–266.

27. Yoshihara S, Yanik G, Cooke KR, Mineishi S. Bronchiolitis obliterans syndrome (BOS), bronchiolitis obliterans organizing pneumonia (BOOP), and other late-onset noninfectious pulmonary complications following allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2007;13(7):749–759.

28. Wong JYC, Filippi AR, Babaja BS, Yahalom J, Specht L. Total body irradiation: guidelines from the International Lymphoma Radiation Oncology Group (ILROG). Int J Radiat Oncol Biol Phys. 2018;101(3):521–529.

29. Quast U. Whole body radiotherapy: a TBI-guideline. J Med Phys. 2006;31(1):5–12.

30. Wolden SL, Rubinovitch RA, Bittner NH, et al. American College of Radiology (ACR) and American Society for Radiation Oncology (ASTRO) practice guideline for the performance of total body irradiation (TBI). Am J Clin Oncol. 2013;36(1):97–101.

31. Beydaegoghlu M, Oysul K, Dirican B, et al. Effect of dose-rate and lung dose in total body irradiation on interstitial pneumonitis after bone marrow transplantation. Tohoku J Exp Med. 2004;202(4):255–263.

32. Sampath S, Schultheis TE, Wong J. Dose response and factors related to interstitial pneumonitis after bone marrow transplant. Int J Radiat Oncol Biol Phys. 2005;63(3):876–884.

33. Crawford SW, Longton G, Storb R. Acute graft-versus-host disease and the risks for idiopathic pneumonia after marrow transplantation for severe aplastic anemia. Bone Marrow Transplant. 1993;12(3):225–231.

34. Hildebrandt GC, Olszewicz KM, Corrion LA, et al. Donor-derived TNF-α regulates pulmonary chemokine expression and the development of idiopathic pneumonia syndrome after allogeneic bone marrow transplantation. Blood. 2004;104(2):586.

35. Merlin TL, Scott DF, Rao MM, et al. The safety and efficacy of laproscopic live donor neoprectomy: a systematic review. Transplantation. 2000;70(12):1659–1666.

36. Burman AC, Banovic T, Kuns RD, et al. IFN-γ differentially controls the development of idiopathic pneumonia syndrome and GVHD of the gastrointestinal tract. Blood. 2007;110(3):1064.

37. Bhalla KS, Polz RJ. Idiopathic pneumonia syndrome after syngeneic bone marrow transplant in mice. Am J Respir Crit Care Med. 2002;166(12):1579–1589.

38. Tizon R, Frey N, Hettjan DF, et al. High-dose corticosteroids with or without etanercept for the treatment of idiopathic pneumonia syndrome after allo-SCT. Bone Marrow Transplant. 2012;47:1332.

39. Yanik G, Hellerstedt B, Custer J, et al. Etanercept (Enbrel) administration for idiopathic pneumonia syndrome after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2002;8(7):395–400.

40. Yanik GA, Ho VT, Levine JE, et al. The impact of soluble tumor necrosis factor receptor etanercept on the treatment of idiopathic pneumonia syndrome after allogeneic hematopoietic stem cell transplantation. Blood. 2008;112(8):3073–3081.

41. Bach PB, Schrag D, Nierman DM, et al. Identification of poor prognostic features among patients requiring mechanical ventilation after hematopoietic stem cell transplantation. Blood. 2001;98(12):3234–3240.

42. Rubenfeld GD, Crawford SW. Withdrawing life support from mechanically ventilated recipients of bone marrow transplants: a case for evidence-based guidelines. Ann Intern Med. 1996;125(8):625–633.

43. See S, Yu J, Jenkins KC, et al. Diagnostic and prognostic plasma biomarkers for idiopathic pneumonia syndrome after hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2018;24(4):678–686.