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Microbiologic Diagnostic Workup of Acute Respiratory Failure with Pulmonary Infiltrates after Allogeneic Hematopoietic Stem Cell Transplantation: Findings in the Era of Molecular- and Biomarker-Based Assays

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A B S T R A C T

Allogeneic hematopoietic stem cell transplantation (HSCT) recipients frequently develop acute respiratory failure (ARF) with pulmonary infiltrates. Molecular- and biomarker-based assays enhance pathogen detection, but data on their yield in this population are scarce. This was a retrospective single-center study of 156 consecutive HSCT recipients admitted to the intensive care unit (ICU) between May 2013 and July 2017. Findings from a microbiologic diagnostic workup using currently available methods on bronchoalveolar lavage (BAL) and blood samples from 66 patients (age, 58 years [range, 45 to 64]; HSCT to ICU, 176 days [range, 85 to 407]) with ARF and pulmonary infiltrates were analyzed. In 47 patients (71%) a causative pathogen was identified (fungal, n = 28; viral, n = 26; bacterial, n = 18). Polymicrobial findings involving several pathogen groups occurred in 20 patients (30%). Culture (12/16, 75%), galactomannan (13/15, 87%), and *Aspergillus*-PCR (8/9, 89%) from BAL but not serum galactomannan (6/14, 43%) helped to diagnose invasive aspergillosis (n = 16, 24%). *Aspergillus*-PCR detected azole resistance in 2 cases. Mucorales was found in 7 patients (11%; BAL culture, n = 6; Mucorales-PCR, n = 1). Patients with identified pathogens had higher Simplified Acute Physiology Score II scores ($P = .049$) and inferior ICU survival (6% versus 37%, $P < .01$), which largely related to the presence of an invasive fungal infection. Eight patients (12%) had 1 or more viruses with uncertain lung pathogenicity as the sole microbiologic finding. A diagnostic microbiologic workup incorporating molecular- and biomarker-based assays identified pathogens in most HSCT recipients with ARF and pulmonary infiltrates admitted to the ICU. Implications of polymicrobial infection and pathogen patterns in these patients warrant further investigation.

INTRODUCTION

Pulmonary complications are a significant contributor to morbidity and nonrelapse mortality after allogeneic hematopoietic stem cell transplantation (HSCT). Acute respiratory failure (ARF) occurs in up to 16% of patients within the first year after HSCT [1] and is the main reason for intensive care unit (ICU) admission in this population [2]. Because of the broad range of possible causative pathogens or noninfectious processes, dedicated algorithms have been proposed to determine the cause of pulmonary infiltrates in immunocompromised hosts [3,4].

In the course of recent decades diagnostic testing has become more sophisticated, and modern approaches now include molecular (eg, PCR) and other nonculture tests (eg, antigen assays) to detect fungal, bacterial, and/or viral pathogens in various types of specimens [5]. In addition to these technical advances, the list of respiratory and opportunistic viruses linked to documented cases of lower respiratory tract disease in immunocompromised hosts has been extended over the last years [6-8]. These developments have led to an increase in the number of diagnosed infections in HSCT recipients

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with ARF that would have previously been diagnosed with a noninfectious post-HSCT lung injury syndrome. In fact, a study was able to identify pathogens in more than half of the cases previously diagnosed with idiopathic pneumonia syndrome using molecular and nonculture tests for a wide array of pathogens on bronchoalveolar lavage (BAL) samples [9]. Still, situations remain where noninfectious post-HSCT lung injury syndromes become the diagnosis of exclusion [10].

In the absence of comparable data in the literature, our study had 2 aims. The first was to analyze the findings of a modern infection detection panel performed on BAL and blood samples in a real-world cohort of critically ill HSCT recipients with ARF and pulmonary infiltrates. Second, we wanted to infer possible clinical and scientific implications.

METHODS

This retrospective study included consecutive adult (ie, ≥18 years old) HSCT recipients treated at the Department of Bone Marrow Transplantation at the University Hospital Essen, Germany. The study was approved by the ethics committee of the University of Duisburg-Essen (EC 15-6446-BO) and conducted in accordance with Good Clinical Practice guidelines and the amended Declaration of Helsinki. Our center performs around 200 adult HSCTs per year in 2 inpatient units with a total capacity of 20 beds. Critically ill patients are treated in a third affiliated unit (ICU) providing 17 closed beds run by trained intensivists and hemato-oncologists.

Consecutive adult HSCT recipients admitted to the ICU between May 2013 (introduction of a PCR-based viral panel for respiratory specimen testing) and July 2017 were screened and included in the study cohort (1) if they had a BAL with available results performed during their ICU stay and (2) if the BAL was conducted as part of a workup of ARF (new requirement of supplemental oxygen or ventilatory support during hospitalization) with pulmonary infiltrates documented on x-ray or computed tomography (CT) of the lungs ±7 days from the procedure.

Data shown in Tables 1 and 2 were obtained by reviewing the patients' medical charts, radiographic images, and discharge letters. Disease risk was categorized according to Seo et al. [11]. The Simplified Acute Physiology Score II (SAPSII) was used to assess the severity of illness at ICU admission [12]. Absolute neutrophil counts and absolute lymphocyte counts were included if results were available ±2 days from BAL.

Standard diagnostic tests performed on BAL included conventional culture for bacteria and fungi; direct microscopy; galactomannan (Bio-Rad, Munich, Germany); PCR testing for the detection of 2 fungal, 3 bacterial, and 20 viral pathogens (*Pneumocystis jirovecii* [Sacace, Como, Italy], *Aspergillus* spp.

Table 1
Cohort Characteristics

	All Patients (n = 66)	Established Pathogen (n = 47)	Without Established Pathogen (n = 19)	*P*
Sex				.29
Male	38 (58)	25 (53)	13 (68)	
Female	28 (42)	22 (47)	6 (32)	
Age at ICU admission, yr	58 (45-64)	58 (47-64)	49 (32-63)	.20
Disease risk at transplantation				.78
Standard	43 (65)	30 (64)	13 (68)	
High	23 (35)	17 (36)	6 (32)	
Cell source				.57
Bone marrow	4 (6)	2 (4)	2 (11)	
Peripheral blood stem cells	62 (93)	45 (96)	17 (90)	
Donor type				.16
Matched related	16 (24)	11 (23)	5 (26)	
Mismatched related	2 (3)	0	2 (11)	
Matched unrelated	36 (55)	26 (55)	10 (53)	
Mismatched unrelated	12 (18)	10 (21)	2 (11)	
Conditioning regimen				.85
MA including TBI ≥ 8 Gy	29 (44)	20 (43)	9 (47)	
MA without TBI	7 (11)	6 (13)	1 (5)	
Reduced intensity	30 (45)	21 (45)	9 (47)	
GVHD prophylaxis				.22
CNI + MTX	52 (79)	36 (77)	16 (84)	
CNI + MMF	10 (15)	9 (19)	1 (5)	
Others	4 (6)	2 (4)	2 (11)	
ATG during conditioning	47 (71)	34 (72)	13 (68)	.77
HSCT to ICU admission, days	176 (85-407)	173 (76-288)	201 (87-415)	.46
ICU during hospitalization for HSCT	14 (21)	11 (23)	3 (16)	.74
SAPSII at ICU admission	38 (27-51)	45 (28-53)	32 (26-39)	**.05***
GVHD during ICU or at admission				
Acute GVHD	16 (24)	10 (21)	6 (32)	.53
Chronic GVHD	18 (27)	14 (30)	4 (21)	.55
Etiology of ARF according to discharge diagnosis				**<.01**
Fungal pneumonia	20 (30)	20 (43)	0	
Viral pneumonia	15 (23)	11 (23)	4 (21)	
Clinically documented pneumonia	15 (23)	3 (6)	12 (63)	
Polymicrobial pneumonia	7 (11)	7 (15)	0	
Bacterial pneumonia	6 (9)	6 (13)	0	
Noninfectious etiology	3 (5)	0	3 (16)	
Life-supporting interventions				
Invasive mechanical ventilation	63 (96)	45 (96)	18 (95)	1.0
P/F ratio at initiation of IMV	167 (129-250)	162 (127-249)	177 (140-253)	.32
Vasopressors	61 (92)	45 (96)	16 (84)	.14
Renal replacement therapy	38 (58)	31 (66)	7 (37)	.05
Extracorporeal life support	12 (18)	8 (17)	4 (21)	.73
ICU length of stay, days	16 (6-27)	14 (5-24)	22 (11-38)	.09
ICU survivors	10 (15)	3 (6)	7 (37)	**<.01**

Values are absolute number (%) or median (IQR). $P < .05$ are shown in bold type. MA indicates myeloablative; TBI, total body irradiation; GVHD, graft-versus-host disease; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; MTX, methotrexate; ATG, antithymocyte globulin; P/F, .

* Exact $P = .049$.