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Clinical Research: Supportive Care

Decline in the Use of Surgical Biopsy for Diagnosis of Pulmonary Disease in Hematopoietic Cell Transplantation Recipients in an Era of Improved Diagnostics and Empirical Therapy



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Historically, diagnosis of enigmatic pulmonary disease after hematopoietic cell transplantation (HCT) required lung biopsy, but recent advancements in diagnosis and therapy for respiratory infections have changed how clinicians approach pulmonary abnormalities. We examined temporal trends in the use of lung biopsy after HCT. We retrospectively reviewed patients who underwent their first allogeneic HCT at the Fred Hutchinson Cancer Research Center between the years 1993 to 1997, 2003 to 2007, and 2013 to 2015 and subsequently underwent surgical lung biopsy for any reason. Lung biopsy between cohorts were analyzed using a Cox proportional hazards model with death and relapse considered competing risks. Of 1418 patients, 52 (3.7%) underwent 54 post-HCT surgical lung biopsies during 1993 to 1997 compared with 24 (2.1%) and 25 biopsies in the 2003 to 2007 cohort; 2 cases of surgical lung biopsies out of 786 HCT recipients occurred during the 2013 to 2015 cohort (.25%). The median time to biopsy post-HCT was 71.5 days (IQR, 31 to 89) for the early cohort and 97 days (IQR, 42 to 124) for the late cohort, for an overall biopsy incidence of .15 and .075 per 1000 patient days in the first year after HCT, respectively. Patients in the 2003 to 2007 cohort were less likely to undergo a lung biopsy (adjusted HR, .50; 95% CI, .29 to .83; $P = .008$) when compared with patients in the early cohort, but more patients in the early cohort underwent lung biopsy without antecedent bronchoscopy (25/54 [46%] versus 3/25 [12%], $P = .005$). Although infections were a more common finding at biopsy in the early cohort (35/1418 versus 8/1148, $P < .001$), the number of biopsies demonstrating noninfectious lesions was similar between the two cohorts (19/1418 versus 17/1148, $P = .76$). Fungal infections were the major infectious etiology in both cohorts (32/35 [91%] versus 5/8 [63%], $P = .07$), but there was a significant reduction in the number of *Aspergillus* species found at biopsy between the cohorts (30/54 versus 1/25, $P < .001$). A similar percentage underwent biopsy with therapeutic intent for invasive fungal disease in the 2 cohorts (8/54 [15%] versus 4/25 [16%]). Surgical evaluation of lung disease in HCT recipients significantly declined over a span of 2 decades. The decline from the years 1993 to 1997 compared with 2003 to 2007 was because of a reduction in the number of biopsies for post-transplant infections due to aspergillosis, which is temporally related to improved diagnostic testing by minimally invasive means and the increased use of empiric therapy with extended-spectrum azoles. This practice of primary nonsurgical diagnostic and treatment approaches to pulmonary disease post-HCT have continued, shown by low numbers of surgical biopsies over the last 3 years.

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INTRODUCTION

Pulmonary complications are frequently encountered in patients undergoing hematopoietic cell transplantation (HCT) and are due to a variety of infectious and noninfectious etiologies, many of which are indistinguishable by either

symptoms or radiologic imaging. Because treatment options vary widely, misdiagnosis can lead to inappropriate therapy, compromise recovery, and lead to excess morbidity and mortality. An aggressive diagnostic approach is essential for the accurate identification of pulmonary complications in these high-risk patients.

Historically, the diagnostic approach of enigmatic lung disease after HCT often led to surgical lung biopsy [1,2]. Surgical lung biopsy has the advantage of being diagnostic as well as therapeutic in some instances, particularly in focally invasive fungal infection. However, improved noninvasive diagnostic modalities for infections have allowed for early diagnosis and detection by less invasive fiberoptic bronchoscopy, thus obviating the need for surgery [3–5]. The emergence of broad-spectrum triazole antifungals and liposomal-lipid complex polyenes in the early 2000s [6,7] have allowed for increased use of less toxic empiric therapy for patients with presumed fungal infections, further limiting the necessity of antecedent lung biopsy. Still, in many situations in which the diagnosis remains uncertain, lung biopsy remains the gold standard for achieving a diagnosis.

The purpose of this study was to examine the temporal trends in the use of surgical lung biopsy in HCT patients as it relates to the emergence of improved diagnostic and therapeutic strategies of invasive fungal disease. In addition, we examined the diagnostic outcomes and the utility of lung biopsy in relationship to bronchoscopy when considering the time period before the routine use more efficacious broad-spectrum triazole antifungal regimens. Finally, we propose a potential strategy for diagnostic workup and decision-making for appropriate use of surgical lung biopsy in HCT.

METHODS

Patients

We reviewed data on patients who received their first allogeneic HCT at the Fred Hutchinson Cancer Research Center (FHCRC) between the years 1993 to 1997 (early cohort) and 2003 to 2007 (late cohort). A third cohort for the years 2013 to 2015 (current cohort) was also reviewed. Recipients who underwent surgical lung biopsy within 1 year (365 days) of HCT were identified from a prospectively collected database of all allogeneic transplant patients as previously described [8]. Additional cases were also identified through pathology records and confirmed by chart review. Cases with incomplete clinical or biopsy data from other institutions were excluded from analysis. The study protocol was approved by the institutional review board of the FHCRC.

Transplant Procedures

Patients received a conditioning regimen followed by infusion of donor cells as determined by the transplant team. After transplant, all patients received immunosuppressive agents as prophylaxis against graft-versus-host disease in the post-transplant period. Standard infectious prophylaxis included acyclovir for herpes simplex virus and/or varicella zoster virus; trimethoprim-sulfamethoxazole, atovaquone, or dapsone for *Pneumocystis jirovecii*; and fungal prophylaxis with fluconazole [9]. All patients received either ceftazidime or levofloxacin for neutropenic prophylaxis [10]. In the later cohort, patients with proven or probable fungal infections [11] or those with pulmonary nodules were more likely to get extended-spectrum azoles (voriconazole and posaconazole). Patients with cytomegalovirus (CMV) infection (on the basis of antigen or DNA testing) were given preemptive therapy with ganciclovir or foscarnet [12].

Pulmonary Evaluation

Patients who developed respiratory symptoms after HCT underwent diagnostic tests including imaging studies (chest radiograph and/or computed tomography of the chest) and laboratory testing, and empiric treatment was ordered at the discretion of the primary service. Subsequent decisions for invasive diagnostic workup, including bronchoalveolar lavage (BAL), fine needle aspiration (FNA), and/or surgical lung biopsy, were made in consultation with the pulmonary, infectious diseases, and thoracic surgery services. If a BAL was performed, all samples were tested for evidence of specific pathogens as listed in Table 1; all specimens also underwent cytopathologic review by a pathologist at the center.

Table 1
Diagnostic Tests Performed on BAL Fluid

Category	Specific Test	Available in 1993–1997	Available in 2003–2007*
Bacterial	Gram stain and culture	+	+
	Acid fast	+	+
	Modified acid fast	+	+
	Modified Gimenez stain	+	+
	Legionella culture	+	+
	Nocardia culture	+	+
	Actinomycoses culture	+	+
Fungal	Giemsa silver stain	+	+
	Pneumocystis DFA	+	+
	Fungal stain and culture	+	+
	Galactomannan	-	+
	Fungal PCR	-	+
Viral	Routine viral culture	+	+
	CMV shell vial	+	+
	CMV rapid DFA	-	+
	Influenza rapid DFA	-	+
	Other human herpesvirus DFAs [†]	+	-
	Other human herpesvirus PCRs [†]	-	+
	Respiratory virus PCRs [‡]	-	+
Other	Periodic acid Schiff stain	+	+
	Cell count and differential	+	+
	Cytologic review	+	+

DFA indicates direct fluorescent antibody.

* The 2013–2015 cohort had similar diagnostic tests performed.

[†] Includes HSV and HHV-6.

[‡] Includes influenza A and B, parainfluenza (1–4), respiratory syncytial virus, human metapneumovirus, bocavirus, coronaviruses, rhinovirus, and adenovirus [4].

Definitions

Pathologic diagnoses were categorized into 3 main categories: infectious, noninfectious, and nondiagnostic. Biopsies were considered nondiagnostic if pathologic findings were nonspecific or if samples were insufficient for diagnosis. Antecedent bronchoscopy with BAL was defined as a bronchoscopy that was performed intentionally for the diagnosis of a pulmonary condition that was ultimately diagnosed or treated by surgical biopsy, before the surgical biopsy. Radiology reports were categorized by specific findings as seen on computed tomography modified from previously published definitions [2,13,14]: focal lesions, which included solitary pulmonary nodule, mass, or consolidation; multifocal infiltrates, masses, or consolidations; and 3) diffuse, which included diffuse ground glass opacities and/or nodular ground glass opacities with >50% of lung involved.

Statistical Analysis

Outcome data were analyzed using Fisher's exact test for categorical variables and Wilcoxon rank-sum for continuous variables. Incidence of surgical biopsy was calculated as the number of biopsies performed per cohort per total number of patient days at risk within 1 year. The cause-specific hazards for lung biopsy within 1 year were compared between the cohorts using a Cox proportional hazards model, where death and relapse were considered competing risks, and adjusted for patient age, severity of disease (low, intermediate, high), and donor type. The statistical software used was SAS, version 9.2 (SAS Institute, Cary, NC).

RESULTS

During 1993 to 1997 (early cohort), 102 chart-verified lung biopsies were performed on 1418 first allogeneic HCT recipients at FHCRC, of which 66 biopsies occurred post-HCT and comprised 54 surgical lung biopsies and 12 FNA among 56 patients. During 2003 to 2007 (late cohort), 56 lung biopsies were performed, including 32 post-HCT biopsies (25 surgical, 7 FNA) in 28 patients. There was 1 pre-HCT transbronchial biopsy in both the 1993 to 1997 and the 2003 to 2007 cohorts but no post-HCT transbronchial biopsies. There were 2 post-HCT surgical lung biopsies and 2 FNA in 4 patients in the current cohort (2013 to 2015). Most surgical biopsies were performed thoracoscopically: 33 of 54 (61%), 19 of 25 (76%), and 2 of 2 (100%) in the early, late, and current cohorts, respectively.

Table 2
Characteristics of the Cohort

Variable	1993–1997		2003–2007		2013–2015	
	Entire* (n = 1418)	Surgical (n = 52)	Entire* (n = 1148)	Surgical (n = 24)	Entire (n = 786)	Surgical (n = 2)
Median age, yr (IQR)	37.4 (25.5–46.6)	33.8 (20.8–46.9)	47.2 (29.3–57)	46.9 (18.2–56)	49.6 (30.1–60.6)	18.4 (17–19.8)
Diagnosis						
ALL	188 (13%)	11 (21%)	116 (14%)	6 (25%)	130 (16.5%)	
AML	352 (25%)	20 (39%)	459 (40%)	9 (43%)	269 (34.2%)	2 (100%)
CML	463 (33%)	9 (17%)	104 (9%)	1 (5%)	19 (2.5%)	
MDS	174 (12%)	5 (10%)	230 (20%)	4 (17%)	0 (0%)	
Other	241 (17%)	7 (13%)		4 (19%)	386 (46.8%)	
Donor						
Matched related	625 (44%)	25 (46%)	443 (39%)	8 (33%)	2 (.001)	0 (0%)
Mismatched related	200 (14%)	10 (19%)	29 (3%)	1 (4%) [†]	256 (32.6%)	0 (0%)
Unrelated	593 (42%)	19 (35%)	676 (59%)	14 (63%)	528 (67.2%)	2 (100%)
Stem cell source						
Bone marrow	1240 (87%)	41 (79%)	227 (20%)	13 (54%)	110 (14%)	0 (0%)
PBSC	158 (11%)	9 (17%)	871 (76%)	9 (38%)	581 (74%)	0 (0%)
Cord blood	9 (1%)	2 (4%)	49 (4%)	2 (8%)	95 (12%)	2 (100%)
GVHD score						
≥2	1076 (77%)	45 (87%)	815 (71%)	18 (75%)	490 (62.3%)	2 (100%)
≥3	421 (30%)	24 (46%)	161 (14%)	6 (25%)	80 (10.1%)	0 (0%)

IQR indicates interquartile range; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; PBSC, peripheral blood stem cell; GVHD, graft-versus-host disease.

* Previously published [8].

[†] Haploidentical donor.

Further analyses of surgical lung biopsies were restricted to the early and late cohorts. A total of 52 of 1418 patients (3.7%) underwent 54 post-HCT surgical lung biopsies during 1993 to 1997 compared with 24 of 1148 patients (2.1%) and 25 biopsies in the 2003 to 2007 cohort. The late surgical cohort was older (median age, 46.9 years [interquartile range, 18.2 to 64.6] versus 33.8 years [interquartile range, 20.8 to 46.9], more likely to have peripheral blood stem cells as their graft source (38% versus 17%), and to have received an unrelated donor graft (63% versus 35%) (Table 2).

The overall surgical lung biopsy incidence within the first year after HCT was .15 and .075 per 1000 patient days, respectively, in the early and late cohorts. Patients in the late cohort were 50% less likely to undergo a lung biopsy (unadjusted hazard ratio, .51; 95% confidence interval, .31 to .82; $P = .006$; adjusted hazard ratio, .50, 95% confidence interval, .29 to .83; $P = .008$) when compared with patients in the early cohort. The median time to biopsy post-HCT was 71.5 days (interquartile range, 31 to 89) for the early cohort and 97 days (interquartile range, 42 to 124) for the late cohort. Although a similar number of patients underwent a bronchoscopy between early and late cohorts (272/1418 [19.2%] versus 243/1148 [21.2%], $P = .15$), more patients in the early cohort underwent lung biopsy without antecedent bronchoscopy (25/54 [46%] versus 3/25 [13%], $P = .005$). A small number of surgical biopsies were preceded by FNA (early, 4/54; late, 3/25). Of note, the number of patients in the current cohort who underwent bronchoscopy after HCT was similar to the other cohorts (171/786, 21.8%).

PATHOLOGIC DIAGNOSES

Infections were more likely to be found at biopsy in the early cohort when compared to the late cohort (35/1418 versus 8/1148, $P < .001$, Figure 1). Most infectious diagnoses in both cohorts (32/35 [91%] versus 5/8 [63%], $P = .07$) were attributed to fungal infections; however, *Aspergillus* species were more common in the early cohort (30/32 [94%]) but accounted for only 20% (1/5) of fungal infections the late cohort (Table 2). The reduction in the number of *Aspergillus* species found at biopsy between the cohorts was significant (30/54

versus 1/25, $P < .001$). Of those biopsies that demonstrated fungal infections, *Mucorales* species were more frequently seen in the late cohort (0/33 [0%] versus 3/5 [60%]). One additional fungal infection caused by *P. jirovecii* was detected by biopsy

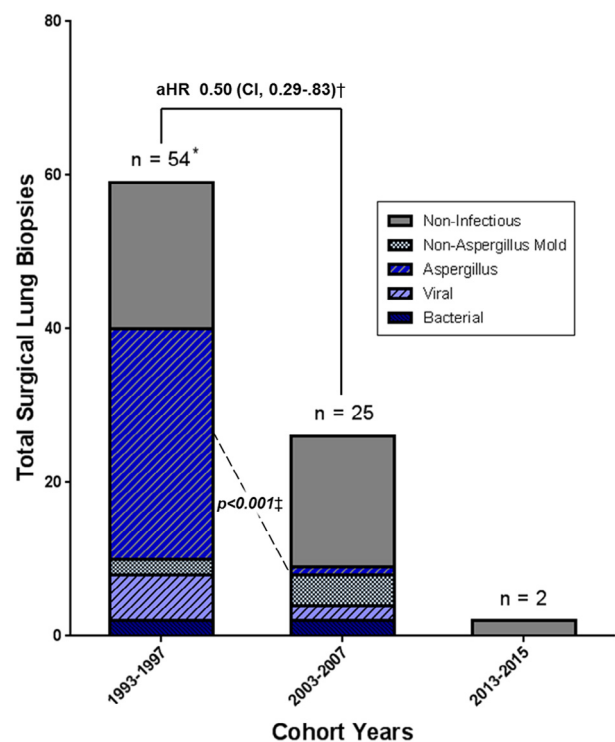


Figure 1. The number of surgical biopsies performed on postallogeic HCT recipients in 3 eras, 1993 to 1997, 2003 to 2007, and 2013 to 2015, broken into diagnostic categories. *Includes 4 cases that were *Aspergillus* and CMV combined diagnosis. Each counted individually in subgroups leading to a total 58 versus total number of biopsies, 54. †Adjusted hazard ratio for surgical lung biopsy between early and late cohort. Adjusted for patient age, severity of disease (low, intermediate, high), and donor type. ‡Comparison of proportion of aspergillosis cases between early and late cohorts.

Table 3
Specific Diagnoses Achieved by Surgical Lung Biopsy, 1993–1997 and 2003–2007

Diagnosis	1993–1997	2003–2007
Infectious		
Aspergillosis	26*	1
Aspergillosis + CMV	4	0
Non- <i>Aspergillus</i> mold	2	4
CMV	0	1
Nocardia	1	0
Bacterial	1†	1
Community respiratory virus	1	1‡
Noninfectious		
Organizing pneumonia (BOOP/COP)	8	6
DAH/IPS	2	2
Diffuse alveolar damage	0	2
Obliterative bronchiolitis	0	1
Malignancy	1	0
Thromboembolism	1	1
Nondiagnostic	7	5

BOOP indicates bronchiolitis obliterans organizing pneumonia; COP, cryptogenic organizing pneumonia; DAH, diffuse alveolar hemorrhage; IPS, idiopathic pneumonia syndrome.

* Including 1 case of aspergillosis concurrent with post-transplant lymphoproliferative disorder.

† *Pseudomonas* concurrent with pulmonary infarct.

‡ Parainfluenza concurrent with thromboemboli.

in the late cohort in a patient who had a prior negative BAL for *P. jirovecii*. Other infectious etiologies established by lung biopsy included *Legionella* spp. and CMV, which was frequently diagnosed concurrently with aspergillosis.

Noninfectious diagnoses made up a significantly larger proportion of the late cohort (19/54 [35%] versus 17/25 [68%], $P = .008$); however, the overall number of biopsies demonstrating noninfectious etiologies was similar between the 2 cohorts (19/1418 versus 17/1148, $P = .76$). In both cohorts the most common specific noninfectious diagnosis was bronchiolitis obliterans organizing pneumonia/cryptogenic organizing pneumonia (early, $n = 8$; late, $n = 6$). Other specific diagnoses included diffuse alveolar hemorrhage, interstitial pneumonia, and obliterative bronchiolitis. Two biopsies in the early cohort and 1 in the late cohort revealed concurrent infectious and noninfectious diagnoses (Table 3). The remainder consisted of nonspecific histology such as diffuse alveolar damage, bronchitis and bronchiolitis, or normal lung (early, $n = 7$; late, $n = 5$).

Of note, in the early cohort 9 of 12 FNAs performed in post-HCT recipients were nondiagnostic. Of the 3 patients in which nondiagnostic FNA was followed by surgical biopsy, all 3 achieved a specific diagnosis. In the late cohort of 7 FNAs, further surgical biopsy was pursued in 2 of the 3 nondiagnostic FNAs and achieved a specific diagnosis. The remaining 4 had specific diagnoses, including *Stenotrophomonas maltophilia*, *Paenibacillus* species, carcinoid, and a case of *Mucorales* infection that was followed by therapeutic surgical resection.

INDICATIONS FOR BIOPSY

Most biopsies in the early cohort were performed for focal lesions (38/54, 70%), whereas most biopsies in the later cohort were performed in patients with multifocal and diffuse disease (18/25, 72%). Of the patients with focal lesions, most were infectious etiologies (early, 32/38 [84%]; late, 4/6 [66%]). Of patients with multifocal disease, there were more noninfectious diagnoses (early, 12/15 [80%]; late, 6/9 [67%]). All patients

with diffuse disease had noninfectious diagnoses (early, 2/2 [100%]; late, 9/9 [100%]).

In some instances the surgical procedure was performed for therapeutic intent for invasive fungal disease, when the diagnosis had been established by bronchoscopy, FNA, or prior surgical biopsy. A similar number of biopsies were done with therapeutic intent in the 2 cohorts (8/54 [15%] versus 4/25 [16%]). In the late cohort, 1 of 4 surgical resections was performed for known aspergillosis and the remaining 3 for disease due to *Mucorales* species, of which 2 had been previously diagnosed by other methods such as FNA as noted above.

DISCUSSION

Advances in the care of HCT recipients in the areas of supportive care, diagnostic testing, and infectious prophylaxis have resulted in improved survival over the past 20 years [8]. Concordant with the use of less toxic conditioning regimens and better long-term outcomes, there is a growing perception that the scope of pulmonary disease has shifted from acute disease early in the post-transplant course to an increase in late noninfectious pulmonary complications [15,16]. The implementation of rapid detection of CMV from BAL fluid in 1988 [3] and preemptive treatment strategies with ganciclovir and foscarnet [17] have led to the decline in incidence and mortality of CMV pneumonia. In addition, major shifts in antifungal treatment and prevention [18] have improved outcomes. Accordingly, we postulated that clinical practices for the diagnosis of HCT-related pulmonary disease have evolved in tandem with recent improvements in diagnostic technologies and treatments aimed at major pulmonary infections. Examination of these practices can shed light into optimal standards of care for clinical practice in a contemporary era of HCT.

Over a 23-year span at our institution, surgical lung biopsies significantly declined in incidence, tended to occur later after HCT, and were associated with a decline of biopsy-proven specific diagnoses of infectious etiologies. In addition, although there was a corresponding increase in the proportion of noninfectious etiologies diagnosed by lung biopsy, the overall number of these cases relative to the total number of patients at risk did not change. The low numbers of surgical biopsies after transplantation in the past 3 years suggests further reduction in the need for surgical diagnosis. In the early cohort, aspergillosis was the most common infectious diagnosis as well as the most common diagnoses overall post-transplant, consistent with well-documented observations that aspergillosis is the most common pulmonary fungal infection affecting HCT patients [19] and that focal lung lesions that persist despite antibiotic therapy are usually fungal [14]. From 2003 to 2007 the decline appeared to be driven almost entirely by the drop in *Aspergillus*-related lung biopsy diagnoses. In addition, there was a shift to performing biopsies on radiographically multifocal and diffuse disease, often linked to primarily noninfectious diagnoses. Diffuse infiltrates after HCT were historically associated with CMV pneumonitis [2], but this diagnosis is now rarely identified on lung biopsy, as confirmed by our data.

The decline in frequency of lung biopsies from the 1990s to the 2000s is likely related to temporal improvements in therapeutic and diagnostic strategies against invasive aspergillosis (Supplementary Figure 1). The third-generation triazole antifungal agent voriconazole was approved for clinical use in 2002 and has subsequently become the first-line treatment against invasive aspergillosis [7] because of its

tolerability, oral bioavailability, and data suggesting enhanced efficacy and an improved toxicity profile when compared with amphotericin B [20]. Other agents in this class, specifically posaconazole and now isavuconazole, have expanded options. Empiric use of voriconazole for suspicious radiographic lesions has become a widely accepted practice, and it is likely that increased use of these agents is directly related to a decrease in the number of biopsies performed.

For diagnosis, the Platelia sandwich ELISA (Bio-Rad, Hercules, CA) for galactomannan has been commercially available in the United States since 2003 for the rapid and noninvasive diagnosis of invasive aspergillosis. Detection of galactomannan in BAL fluid is highly sensitive in HCT recipients and is more sensitive than serum galactomannan particularly in neutropenic patients [21]. Together, serum and BAL galactomannan diagnoses have increased our ability to identify *Aspergillus* [22], allowing patients to receive highly effective therapy.

Because of this assay and other advances in microbiologic diagnostics (eg, PCR testing [4]), bronchoscopy has supplanted surgical lung biopsy as the first-line invasive diagnostic procedure for the evaluation of pulmonary lesions in HCT recipients. Early diagnostic bronchoscopy is now recommended over empiric treatment in HCT recipients with evidence of specific pulmonary processes [23] and is likely to have higher yield when clinical suspicion of infection is high [24]. This shift in practice is illustrated by the increasing proportion of lung biopsy recipients who underwent an antecedent bronchoscopy with BAL in the late cohort compared with the early cohort. As a consequence, the cohort of patients who underwent surgical lung biopsy performed in the latter cohort are likely to be a highly selected group for whom empiric therapy with anti-infective agents did not improve the infiltrates, bronchoscopy did not yield a diagnosis, or surgery was performed for therapeutic intent. Most surgical procedures for fungal disease were performed for therapy of established *Mucorales* spp. infection, which were the most common invasive fungal disease in the late cohort. This epidemiology is consistent with the use of empiric voriconazole compared with the early cohort, given that *Mucorales* spp. are not susceptible to voriconazole [25].

Although a number of biopsies did not identify a specific etiology, the identification of specific diagnoses for which there is treatment, such as cryptogenic organizing pneumonia, suggests that surgical lung biopsy during 2003 to 2007 was useful when patients failed prophylaxis or empiric therapy for infections and had a negative BAL evaluation. The rarity of lung biopsy in the current cohort of 2013 to 2015 suggests that a BAL that does not identify an infectious etiology may be sufficient for a clinician to begin empiric therapy for a presumptive infection or for a noninfectious pulmonary complication. Of note, there were no transbronchial biopsies in the post-HCT time frame in our cohort. At our center, transbronchial biopsies are rarely performed in HCT recipients because transbronchial biopsies lead to more complications than unique diagnoses when BAL is nondiagnostic [26,27].

Although analysis of the incidence of post-HCT noninfectious pneumonia is beyond the scope of this study, it is likely that collective experience with typical radiographic features of cryptogenic organizing pneumonia after HCT [28] in an appropriate clinical setting in the absence of infection has obviated the need for a surgical lung biopsy. However, when the radiographic features are uncharacteristic of organizing

pneumonia or the potential complications from corticosteroids outweigh the benefits of empiric treatment, a surgical lung biopsy may still be required to establish a firm diagnosis.

Although detailed analysis of FNA, a minimally invasive alternative to surgery for obtaining tissue, was not the aim of this study, it is worth noting that the overall use of this modality was low in our cohort. FNA has been shown to have a relatively high yield in HCT recipients specifically for aspergillosis [14,29], particularly in peripheral focal lesions; however, a systematic analysis of this modality has not been performed since the introduction of broad-spectrum triazoles and galactomannan testing. The decision to refer a patient for FNA is likely due to a number of factors that vary from institution to institution, including the availability of interventional radiology, the location of the specific lesion, and clinician bias regarding the risk-to-benefit ratio, particularly in the setting of thrombocytopenia. The small number of FNAs may also reflect the decline in cases of aspergillosis. The number of cases in our cohort is too small to draw specific conclusions about the utility of FNA, which is likely to be of highest yield when the lesion is focal, peripheral, and of sufficient size [30] to obtain adequate material for both pathology and microbiologic culture.

The value of surgical lung biopsy is highest when the benefit of achieving a specific diagnosis outweighs the surgical risks in this population [13] and when surgery is potentially therapeutic, as in the case of suspected invasive fungal infection unresponsive to standard therapy. Distinguishing between infectious and noninfectious etiologies when empiric therapies fail is a critical step in deciding whether to continue, withhold, or change therapy, particularly when nonaspergillus mold species are suspected. Video-assisted thoracoscopic surgery, which was introduced in the early 1990s, has reduced the morbidity associated with open lung biopsy and is now accepted and widely used for diagnostic and therapeutic purposes [31]. In situations when clinical judgment is equivocal and less invasive means are uninformative, surgical biopsy should be considered. We propose an algorithm to aid in the workup of pulmonary abnormalities after HCT, shown in Figure 2. This reflects the current practice at our institution and is consistent with studies investigating the yield of BAL and lung biopsy in this population [24]. Although this algorithm is based on radiographic patterns, the clinical context and clinical suspicion for a specific diagnosis and clinical feasibility of performing bronchoscopy (ie, patient characteristics, location and size of the lesion) will dictate the diagnostic workup and/or empiric management. Voriconazole is generally chosen as the first-line empiric therapy in cases of pulmonary nodules because of the frequency of aspergillosis and availability and ease of administration of the drug. Newer tablet formulations of posaconazole, which has improved bioavailability and activity against some *Mucorales* spp., may also be considered as an option for empiric therapy.

Our study is limited by its single-center and retrospective design. Diagnostic practices in the evaluation of lung disease and use of empiric antifungals for pulmonary nodules vary from institution to institution, given the availability of specific tests, frequency of bronchoscopy, and medical practitioners who have experience in performing lung biopsy on this specialized population of immunocompromised patients. This study reflects a large academic center with a high-volume HCT practice, pulmonary services with experience with BAL in HCT, and with availability of center-specific microbiologic tests such as fungal PCR. The utilization of surgical

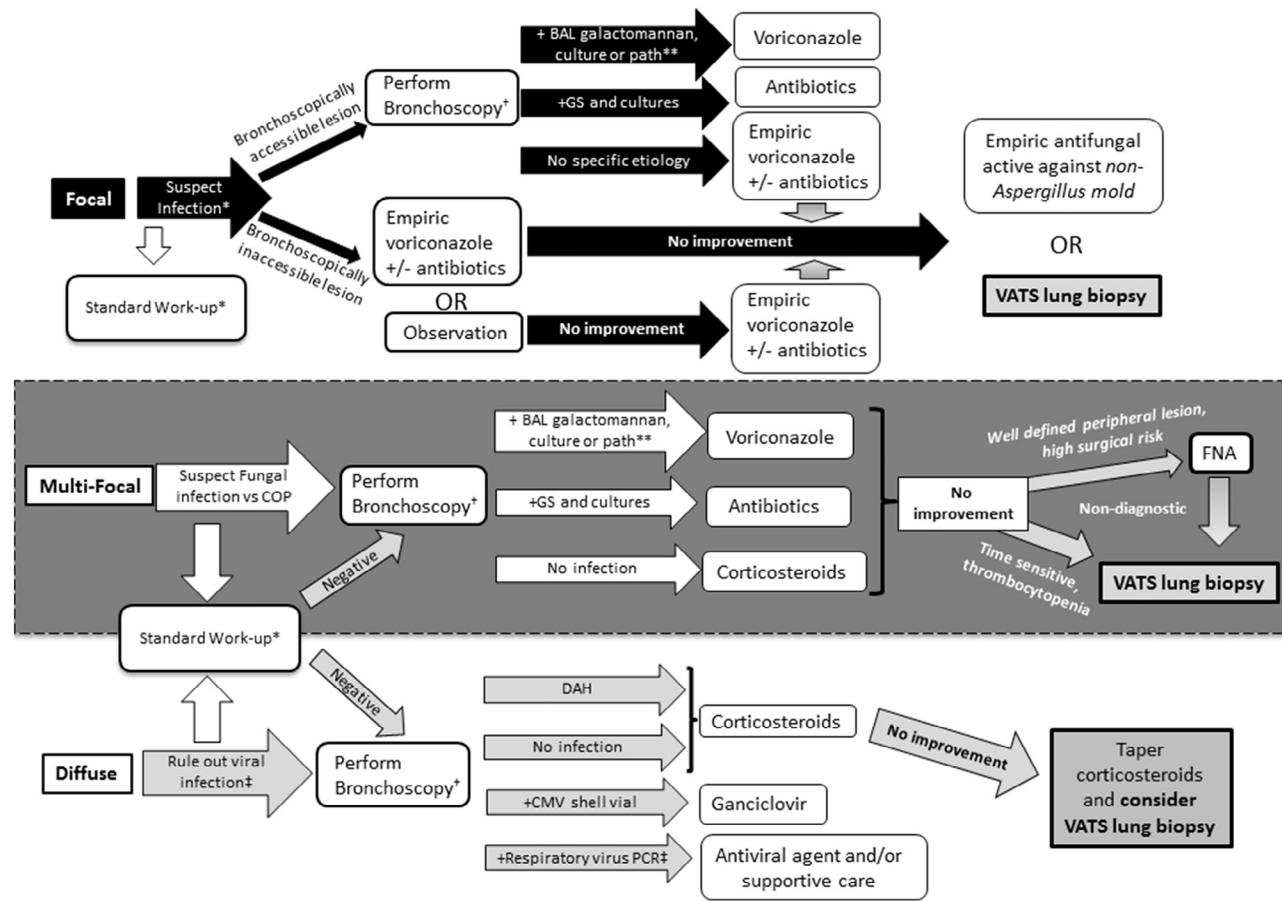


Figure 2. Suggested algorithm for management of abnormal pulmonary findings after allogeneic HCT, based on initial CT scan findings and clinical suspicion. *Standard workup includes serum galactomannan, respiratory virus panel, and/or other blood work; sputum cultures can be considered but often of very low yield. †See Table 1 for tests commonly sent from bronchoscopy. ‡Respiratory viral panel dependent on panel availability: the panel at FHCRC includes PCR for influenza A/B, respiratory syncytial virus (RSV), parainfluenza viruses (1–4), coronavirus, rhinovirus, adenoviruses, metapneumovirus, and bocavirus. Of note, respiratory viral DFA and PCR tests as outlined in Table 1 should be sent on nasopharyngeal swab samples as well as BAL. **Meets criteria for probable aspergillosis [11]. GS indicates Gram stain; VATS, video-assisted thoracoscopic surgery; DFA, direct fluorescent antibody; DAH, diffuse alveolar hemorrhage; COP, cryptogenic organizing pneumonia; CMV, cytomegalovirus.

lung biopsy observed in this study may not be applicable to clinical practice settings in which the experience with HCT is limited and those where surgical lung biopsy may be the primary means of achieving a diagnosis. In addition, this diagnostic algorithm presented must also be taken into context with local diagnostic testing options and geographic fungal epidemiology patterns. As is the case with any endpoint that rests on a clinical decision, the results may be simply based on the biases of the physician or group of physicians encountered by the patient.

In summary, diagnostic practices for lung disease have evolved to reflect the changing epidemiology of opportunistic infections after HCT as well as the collective experience in empiric management of noninfectious complications. As a consequence of improved outcomes from aspergillosis, the burden of pulmonary pathology has shifted to late noninfectious complications, which is an area of unmet need in this population. Additionally, nodules due to invasive fungal disease and unresponsive to empiric therapy are largely caused by non-*Aspergillus* species. These observations suggest a need for further investigation into minimally invasive means of diagnosing noninfectious pulmonary complications, improved diagnostic tools, and more efficacious treatment for these important late pulmonary complications after HCT.

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SUPPLEMENTARY DATA

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