

Invasive *Aspergillus* infections in hospitalized patients with chronic lung disease

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Background: Although invasive pulmonary aspergillosis (IPA) is more prevalent in immunocompromised patients, critical care clinicians need to be aware of the occurrence of IPA in the nontraditional host, such as a patient with chronic lung disease. The purpose of this study was to describe the IPA patient with chronic lung disease and compare the data with that of immunocompromised patients.

Methods: The records of 351 patients with *Aspergillus* were evaluated in this single-center, retrospective study for evidence and outcomes of IPA. The outcomes of 57 patients with chronic lung disease and 56 immunocompromised patients were compared. Patients with chronic lung disease were defined by one of the following descriptive terms: emphysema, asthma, idiopathic lung disease, bronchitis, bronchiectasis, sarcoid, or pulmonary leukostasis.

Results: Baseline demographics were similar between the two groups. Patients with chronic lung disease were primarily defined by emphysema (61%) and asthma (18%), and immunocompromised patients primarily had malignancies (27%) and bone marrow transplants (14%). A higher proportion of patients with chronic lung disease had a diagnosis of IPA by bronchoalveolar lavage versus the immunocompromised group ($P < 0.03$). The major risk factors for IPA were found to be steroid use in the chronic lung disease group and neutropenia and prior surgical procedures in the immunocompromised group. Overall, 53% and 69% of chronic lung disease and immunocompromised patients were cured ($P = 0.14$); 55% of chronic lung patients and 47% of immunocompromised patients survived one month ($P = 0.75$).

Conclusion: Nontraditional patients with IPA, such as those with chronic lung disease, have outcomes and mortality similar to that in the more traditional immunocompromised population.

Keywords: *Aspergillus*, moulds, intensive care units, chronic lung disease, antifungals

Introduction

Identification and treatment of systemic fungal infections has increased over the last two decades,¹ in part due to improved care of immunocompromised patients, including those with human immunodeficiency virus infection and those receiving hematopoietic stem cell transplantation. In the 1980s and early 1990s, infections due to *Candida* species were prevalent, but largely because of the introduction of azoles and liposomal polyenes, *Candida albicans* infections were successfully treated; however, non-*C. albicans* infections (notably, *C. glabrata* and *C. parapsilosis*) were found to occur at an increased rate.^{2,3} Recently, the incidence of *Aspergillus* and other moulds, including rare and refractory moulds (eg, *Scedosporium*, *Fusarium*, and *Zygomycetes*), have been documented in the literature.⁴⁻⁷ Previously, these infections were seen only in the immunocompromised population. However, recent reports have described

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invasive pulmonary aspergillosis in intensive care patients with an intact immune system complicated with serious comorbidities, such as chronic lung disease, cirrhosis, and prior surgical procedures.^{8–13}

This is a report comparing patients with *Aspergillus*, whether colonized or infected, who have an apparently intact immune system, with those who are immunocompromised from a comprehensive patient database at a tertiary care trauma center in the United States. This paper seeks to define the characteristics of our patients who do not have the traditional hallmarks of a compromised immune system and yet still develop clinical aspergillosis.

Methods and materials

Sampling of patients

We collected deidentified data from a large database of hospitalized patients at the University of Massachusetts Memorial Healthcare System (Worcester, MA, USA) who had *Aspergillus* infection. Diagnosis of patients with proven or probable invasive *Aspergillus* infection was done using the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria.^{14,15}

The following information was collected: patient demographics (age, gender, ethnicity), comorbidities (chronic lung disease, diabetes, cancer, rheumatoid arthritis, liver disease; Charlson comorbidity index¹⁶), culture results, treatment regimens, and clinical outcomes. Neutropenia was defined as an absolute neutrophil count < 1000 cells/ μ L. Chronic lung disease was defined by the diagnosis of emphysema, chronic obstructive pulmonary disease (COPD), asthma, idiopathic lung disease, chronic bronchitis not of bacterial etiology, bronchiectasis, sarcoid, or pulmonary leukostasis at admission. Patients with a diagnosis of allergic bronchopulmonary aspergillosis were excluded from evaluation. The immunocompromised population was defined as having active aspergillosis without chronic lung disease at baseline.

An independent review panel consisting of two infectious disease physicians and one critical care physician reviewed the deidentified database blinded for treatment to determine outcome (clinical versus failure) based upon criteria established by the Infectious Diseases Society of America.¹⁷ This study was performed with the prior approval of the University of Massachusetts human subjects committee under a waiver of the requirement for informed consent.

Statistical analysis

Post hoc analyses were conducted on the final locked database following resolution of all queries. Comparative statistical

analysis between the chronic lung disease group and the immunocompromised patient population was performed for demographics, comorbidities, treatment regimens, and clinical outcomes, including mortality. The Student's *t*-test was performed for continuous variables and Fisher's Exact test was performed for categorical variables. Statistical significance was defined as $P \leq 0.05$ with a two-sided *t*-test. Data analyses were conducted using Statistical Analysis System (SAS Institute, Cary, NC, USA) version 9.2.

Results

A total of 351 patients with culture-positive *Aspergillus* from a sterile compartment were identified from the patient database over a seven-year period from August 2002 to April 2009. Of these, 238 (68%) patients were considered to be colonized with *Aspergillus* and the remaining 113 (32%) patients were culture-proven for active *Aspergillus* infection (Figure 1). Half of these patients ($n = 57$) had a comorbidity of chronic lung disease and the other half ($n = 56$) were immunocompromised other than by using systemic steroids (defined as traditional hosts of aspergillosis).

Consistent with the EORTC/MSG criteria,¹⁴ confirmation of culture-positive *Aspergillus* was made in the sputum of 53% of the patients with chronic lung disease and 21% of the immunocompromised population; 37% and 16%, respectively, in bronchoalveolar lavage samples; 11% and 36%,

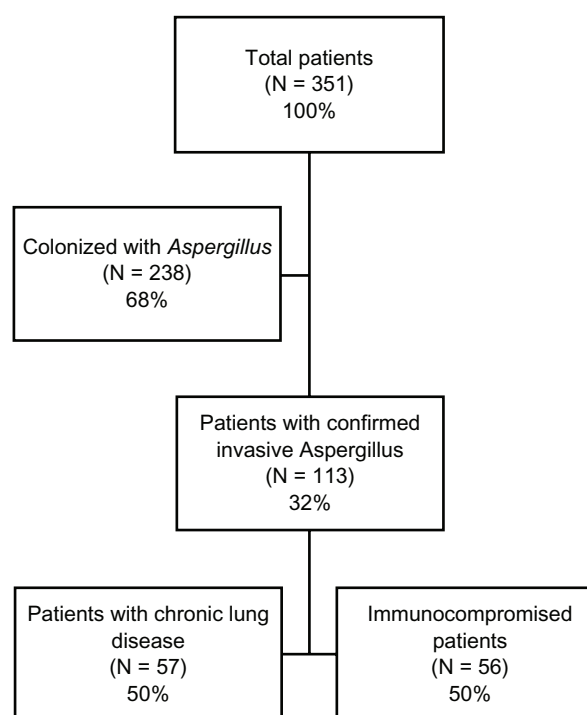


Figure 1 Patient selection.

respectively, in other sterile sites; and no evidence of fungemia in the 38 and 24 patients, respectively, drawn for blood cultures.

Table 1 summarizes the baseline patient characteristics of those with chronic lung disease compared with those who were immunocompromised. Demographics between the two groups were similar, but there were a disproportionately greater number of patients with liquid tumors (eg, leukemia, lymphoma), bone marrow transplants, and a diagnosis of human immunodeficiency virus or acquired immunodeficiency syndrome in the immunocompromised group. In contrast, and consistent with their underlying pathology, there were more patients with chronic lung disease who had bronchoalveolar lavages culture-positive for *Aspergillus*. The majority of patients with chronic lung disease had a diagnosis of emphysema (61%) or asthma (18%; Table 2). Forty-four (77%) patients presented with cough as the primary symptom compared with 15 (27%) immunocompromised patients ($P < 0.0001$). The seven patients in the chronic lung disease group with a comorbidity of liquid tumor, including one with a successful bone marrow transplant, were not immunocompromised.

Neutropenia was more prevalent in the immunocompromised patients than in those with chronic lung disease (19.6% versus 8.8%; $P = 0.11$). The Charlson comorbidity index was similar between the two groups, with a slightly greater risk of dying in patients with aspergillosis and chronic lung disease. Risk factors for invasive pulmonary aspergillosis were prior surgical procedures and neutropenia in the

immunocompromised group and chronic steroid use in those with chronic lung disease (Table 1).

Table 3 describes the primary pathogen identified at baseline between the two groups and differences in all-cause mortality. *Aspergillus fumigatus* was the most prevalent species identified at baseline in either group, with a higher incidence of all-cause mortality found in the immunocompromised patients.

Table 4 describes outcomes of each group by treatment. Voriconazole was used to treat twice the number of patients with chronic lung disease (62%) compared with immunocompromised patients (31%). Of interest was not only the differences in treatment patterns between the two groups but also that 10 patients (six with chronic lung disease, four immunocompromised) did not receive any treatment for invasive pulmonary aspergillosis. Most of these patients ($n = 5$) were due to late recognition of this infection and two patients were established to have a terminal condition and the families decided on comfort measures only. Three patients died either as a consequence of their infection or underlying comorbidity (Table 4). The time course of all-cause mortality was similar between the two treatment groups ($P = \text{NS}$; Figure 2).

Discussion

The traditional setting for an *Aspergillus* infection is in a patient with host defense defects, whether through cellular (eg, monocyte/macrophage), mechanical (intravenous catheters), or medication (corticosteroids, anti-T lymphocyte

Table 1 Mean baseline characteristics of patients with chronic lung disease and immunocompromised patients

	Chronic lung disease n = 57	Immunocompromised patients n = 56	P value
Age, years	63.1 (15.9)	52.9 (13.6)	0.26
Male, n (%)	25 (43.9)	35 (62.5)	0.06
Race, white, n (%)	38 (66.7)	27 (48.2)	0.28
Charlson comorbidity index			
• Low/medium points, n (%)	31 (54.4)	36 (64.2)	0.32
• High/very high points, n (%)	26 (45.6)	20 (35.7)	0.34
Comorbidities, n (%)			
• Solid tumor	0	11 (19.6%)	<0.0001
• Liquid tumor	7 (12.3%)	16 (28.6%)	0.04
• Diabetes	10 (17.5%)	8 (14.3%)	0.79
• BMT	1 (1.7%) ^a	8 (14.3%)	0.02
• HIV/AIDS	0	5 (8.9%)	0.03
Positive BAL, n (%)	21 (70%)	9 (37.5%)	0.03
Risk factors, ^b n (%)			
• Prior surgical procedure	5 (8.8%)	25 (44.6%)	<0.0001
• Steroids	31 (54.4%)	8 (14.3%)	<0.0001
• Neutropenia ^c	5 (8.8%)	11 (19.6%)	0.11

Notes: ^aOne patient had a liquid tumor treated with BMT; ^bfor invasive pulmonary aspergillosis; ^cabsolute neutrophil count < 1000 cells/μL.

Abbreviations: BAL, bronchoalveolar lavage fluid; BMT, bone marrow transplantation; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

Table 2 Presenting symptoms of patients with chronic lung disease by primary diagnosis

Primary diagnosis	n (%)	Presence of symptom, n (%)					
		Cough	Fever	Hemoptysis	Weight loss	Shortness of breath	Chest pain
Emphysema	35 (61%)	27 (77%)	11 (31%)	2 (6%)	6 (17%)	28 (83%)	7 (20%)
Asthma	10 (18%)	8 (80%)	0	0	0	8 (80%)	3 (30%)
Bronchiectasis	5 (9%)	5 (100%)	0	1 (20%)	0	4 (80%)	1 (20%)
Other ^a	7 (12%)	4 (57%)	3 (43%)	2 (29%)	2 (29%)	6 (86%)	1 (14%)

Notes: ^aIdiopathic lung disease (n = 2), sarcoid (n = 2), bronchitis (n = 1), bronchiolitis obliterans with organizing pneumonia (n = 1), and pulmonary leukostasis (n = 1).

therapy) defects.¹⁸ For example, there is a high prevalence of fungal infections, in particular moulds, in patients who have undergone hematopoietic stem cell transplantation. The disrupted immune system secondary to chemoablation and radiation often results in bacterial and fungal infections in the early pre-engraftment phase (< 15 to 45 days following transplantation). Fungal infections also occur in the post-engraftment phase (30–100 days following transplantation), primarily due to impaired cell-mediated immunity.¹⁸ In addition, the widespread use of fluconazole and other first-generation azoles has resulted in selection for mould infections because this class of drugs effectively treats systemic yeast infections but not moulds. Other risk factors for mould infections include disruption of the environment (eg, recent construction), use of high-dose or prolonged courses of corticosteroids, prior surgical procedures, and immunologic disorders, such as acquired immunodeficiency syndrome and autoimmune diseases.¹⁹

We report on the unexpectedly high incidence of *Aspergillus* in patients not considered traditional hosts for these types of infections. These “nontraditional” hosts include those with chronic lung disease, as noted in our study, and also patients in the intensive care setting who may not have chronic lung disease nor an immunocompromised system.²⁰ Meersseman et al²¹ described proven or probable invasive aspergillosis in 67 intensive care patients without malignancy; half of these patients had a diagnosis of COPD and the vast majority (94%) had received steroids after admission to the intensive care unit. Mortality in this study was 91%, independent of treatment and whether the infection was proven or probable. Other factors that predispose the

non-neutropenic intensive care patient to mould infections include advanced liver disease, chronic renal replacement therapy, mechanical ventilation, diabetes mellitus, surgery, and near-drowning.^{21–23} It has been postulated that better intensive care procedures and prolonged patient survival have significantly contributed to the increased incidence of invasive pulmonary aspergillosis.²⁰

The association between chronic lung disease and *Aspergillus* infections dates back more than three decades when it was first described in horses. Animals with COPD were found to express precipitating antibodies to *A. fumigatus* more frequently.²⁴ Case reports surfaced in the clinical literature shortly thereafter, describing high mortality most likely due to delayed diagnosis and relatively poor treatment options for aspergillosis.^{25–33} Whereas mortality and morbidity were attributed to prolonged and high-dose treatment with corticosteroids,³⁴ the clinician should also suspect *Aspergillus* as the possible cause of progressive respiratory failure in the presence of short-term steroid therapy.^{35,36} It is tempting to speculate that patients with chronic lung disease should be considered traditional hosts due to the high incidence of steroid use in this population. Steroids increase the risk of infections, but the clinician generally considers bacterial and not fungal infections as the cause for the persistent pneumonia. Our data show that more of the patients with chronic lung disease used steroids, which may explain why this patient subset is susceptible to invasive pulmonary aspergillosis, although these patients are not the traditional immunocompromised population. It is important to be aware of the possibility of fungal infection and take precautions.

Table 3 All-cause mortality by *Aspergillus* species identified at baseline between treatment groups

Species	Chronic lung disease	Mortality	Immunocompromised	Mortality
<i>Aspergillus fumigatus</i>	33 (71.7%)	15 (53.6%)	19 (55.9%)	13 (81.3%)
<i>Aspergillus flavus</i>	4 (8.9%)	1 (33.3%)	2 (5.9%)	0 (0.0%)
<i>Aspergillus niger</i>	2 (4.4%)	0	7 (20.6%)	0
<i>Aspergillus terreus</i>	1 (2.2%)	0	2 (5.9%)	0
Other	2 (4.4%)	0	2 (5.9%)	0
Mixed	4 (8.7%)	2 (50.0%)	2 (5.9%)	1 (50.0%)

Table 4 Outcome by treatment according to group

Treatment	Chronic lung disease			Immunocompromised		
	n	Cure ^a	Mortality ^b	n	Cure ^a	Mortality ^b
Voriconazole	29	15 (51.7)	12 (41.4)	12	6 (50.0)	6 (50.0)
Itraconazole	7	4 (57.1)	1 (14.3)	1	1 (100.0)	1 (100.0)
Amphotericin B	1	0 (0.0)	1 (100.0)	2	1 (50.0)	1 (50.0)
Other ^c	4	3 (75.0)	1 (25.0)	20	13 (65.0)	8 (40.0)
No treatment	6	3 (50.0)	2 (33.3)	4	4 (100.0)	1 (25.0)

Notes: ^aCure was determined by an independent review panel; ^ball-cause mortality; ^cother includes caspofungin, micafungin, posaconazole, combination therapy, and not otherwise specified therapy.

It is interesting to note that the patients with chronic lung disease had outcomes similar to those in the immunocompromised group. Historically, nontraditional hosts have worse outcomes once a diagnosis of invasive pulmonary aspergillosis has been made.^{8,37,38} Early diagnosis is a prognostic factor for a positive outcome in patients with invasive pulmonary aspergillosis,^{39,40} but the diagnosis is often delayed either due to lack of awareness or it is difficult to establish due to insensitive and/or nonspecific assay methodologies.⁴¹ Once suspected, the clinician should examine for radiologic evidence of an infection (chest x-ray, computed tomography), obtain respiratory secretions and/or tissue biopsies for culture, and determine the galactomannan concentration in either blood or bronchoalveolar fluid. Recently, galactomannan, a component of the cell wall of *Aspergillus*, has been studied as an early marker of invasive pulmonary aspergillosis.^{42–46}

We did not evaluate galactomannan in our study. Nonetheless, there are limited data suggesting that galactomannan levels in the blood or bronchoalveolar lavage fluid may have diagnostic and prognostic value in patients with invasive pulmonary aspergillosis.⁴³

This study has limitations that should be considered when interpreting the data. It is a nonrandomized observational study of patient data extracted over a seven-year period at an academic medical center with policies that mandate involvement of infectious disease experts for cases involving administration of intravenous antifungals for nearly all patients, including those in the intensive care unit. This practice allows for common decision-making per established institutional guidelines; however, treatment of these infections in our study were varied by the use of triazoles, polyenes, and echinocandins. For example, we could not identify the drug susceptibility of the infecting organism, yet we know that 19 patients with aspergillosis were treated with a drug (eg, fluconazole, echinocandin) that is not indicated for the primary treatment of aspergillosis. Further, there was no reason documented in the charts of the three patients with a diagnosis of proven or probable invasive pulmonary aspergillosis who did not receive any systemic antifungal therapy. The doses and duration of steroids were not consistent with each patient in the study. As mentioned previously, *Aspergillus* infections have been diagnosed in patients following either

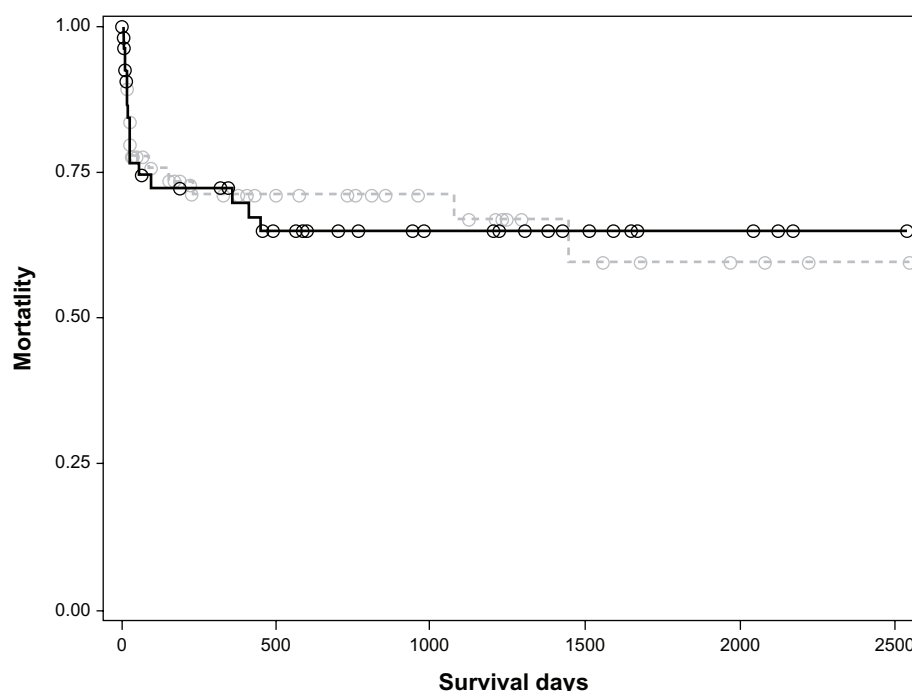


Figure 2 Kaplan-Meier plot of all-cause mortality by time of those patients with chronic lung disease (—) and immunocompromised patients (---).

short-term or long-term courses of steroids at various dosages and regimens.

There was a disproportionate number of patients in both groups treated with voriconazole compared with other systemic antifungals. Voriconazole has broad coverage of both yeast and moulds and may have been started empirically in the absence of a definitive diagnosis.¹⁰ Nonetheless, our study may be more informative than randomized controlled trials in that it reflects current clinical practice, given that no patient cases were excluded.

Whether the outcomes data were dissected by species or by treatment (Tables 3 and 4), we found comparable mortality rates in the chronic lung disease (37% and 36%) and immunocompromised (41% and 44%, respectively; Figure 2) populations. It is important to note that mortality in the immunocompromised group would not only be due to invasive pulmonary aspergillosis but also to the underlying conditions, such as human immunodeficiency virus, tumors, and chemotherapy. Therefore, it is unlikely to be true that the two groups of patients have similar mortality rates, and our study may have had too few patients to understand the true mortality rates in larger populations.

The primary observation of our study is that there are risk factors for invasive pulmonary aspergillosis in the intensive care patient other than an immunocompromised state. We evaluated the incidence of invasive pulmonary aspergillosis in patients with chronic lung disease and compared the results with a cohort of immunocompromised patients. We identified prior surgical procedures and neutropenia (absolute neutrophil count < 1000 cells/ μ L) as risk factors in the immunocompromised population; the use of steroids was associated with greater risk for invasive pulmonary aspergillosis in patients with chronic lung disease. Whereas the diagnosis of aspergillosis is often difficult to establish, persistent pneumonia that is nonresponsive to appropriate antibacterial treatment should alert the clinician to a fungal origin. More rapid diagnosis and appropriate treatment with a broad-spectrum antifungal may lower the high incidence of morbidity and mortality previously associated with this nontraditional host population.

Disclosure

These data were presented in part at the 48th Annual Meeting of the Infectious Disease Society of America, Vancouver, British Columbia, Canada, held on October 21–24, 2010. DRL and VLW were employees of Pfizer Pharmaceuticals at the time of this study. MW is an employee and AS and TB are medical interns at the University of Massachusetts with no financial competing interests. All analyses were

performed with a database blinded to comorbidities and treatment allocations.

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