

Aspergillus Infections After Lung Transplantation

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Abstract: Invasive fungal infections are a serious consequence of organ transplantation. We observed an increase in *Aspergillus* infections at our institution among lung transplantation recipients in the year 2000. Records of patients undergoing lung transplantation between 1999 and 2001 were analyzed for evidence of *Aspergillus* colonization or infection, and potential risk factors for infection were identified. Twenty *Aspergillus* infections were identified in 103 lung transplant recipients. Thirteen patients had tracheobronchitis, and 7 had invasive pulmonary aspergillosis. Nineteen patients were colonized with *Aspergillus*. One half of all *Aspergillus* infections occurred during 2000. There were no differences in demographic or surgical variables, underlying medical illness or postoperative care in association with *Aspergillus* infection. Factors classically associated with aspergillosis were not found to correlate with an increased risk of infection. Only a specific period of transplantation was significantly associated with *Aspergillus* infection, suggesting an increased environmental exposure during that period.

(*Infect Dis Clin Pract* 2006;14:283–288)

Infection remains an important cause of morbidity and mortality among solid organ transplant recipients, including those receiving lung allografts. Most of the infections occurring in the initial weeks after transplantation are due to nosocomial bacterial pathogens. Although less common than bacterial infections in the early postoperative period, invasive fungal infections account for a disproportionate number of deaths. Invasive aspergillosis, with a mortality rate of more than 50% despite appropriate therapeutic intervention, is the cause of many of these deaths.^{1,2}

Lung transplant recipients appear particularly vulnerable to aspergillosis, with 8.4% experiencing invasive *Aspergillus* infection among a review of 645 patients.³ This rate may be elevated after increased environmental exposure to the fungus, as can occur during hospital renovation.^{4–6}

The rate of *Aspergillus* infection in lung transplant recipients exceeds that of all other solid organ transplants and is compared with the rates seen in bone marrow transplantation.^{3,7} Increased susceptibility to infection among lung transplant recipients is probably multifactorial, related to the host's impaired immunity and local factors unique to lung transplantation. Perhaps most important is the allograft's continuous exposure to the environment, allowing inhaled fungal spores direct access to the lung. Further vulnerability may be due to an impaired cough reflex, decreased mucociliary clearance, and vascular inadequacy at the anastomotic site.⁸

To clarify the risk factors for *Aspergillus* infection in the early postoperative period after lung transplantation, the medical records of patients undergoing lung transplantation at our institution over a 3-year period were reviewed.

MATERIALS AND METHODS

The University of Michigan Health System is an 800-bed tertiary care hospital with an active pulmonary medicine and lung transplantation service. One hundred and five lung transplants occurred during the study period, with most of the operations performed by a single surgeon. A retrospective cohort study was performed for all adult patients who underwent primary lung transplantation at our institution between January 1999 and December 2001. Data were collected from the transplant service database, infection control and microbiology departments, and medical records.

Aspergillus colonization was defined as isolation of an *Aspergillus* species from sputum or bronchoalveolar lavage (BAL) specimen in the absence of clinical, radiographic, endoscopic, or histological evidence of disease at any time during the period 60 days after transplantation. *Aspergillus* tracheobronchitis (TB) was defined as isolation of *Aspergillus* from bronchoscopy specimen or histological evidence of fungal invasion in a patient with endobronchial abnormalities and no alternative diagnosis. Invasive aspergillosis (IA) was defined as a positive culture for *Aspergillus* species or histological evidence of tissue invasion by *Aspergillus* (acutely branching septate hyphae) and pulmonary parenchymal infiltrates, nodules, or cavitory lesions not attributable to another cause. Any patient that initially was colonized with *Aspergillus* but developed evidence of TB or IA within 60 days of transplant was classified as being in the infected rather than colonized group. All records were reviewed for the presence of *Aspergillus* isolates from the time of transplant to 60 days postoperatively.

Posttransplant immunosuppression included corticosteroids (methylprednisolone 200 mg/d postoperatively changed to prednisone 0.5 mg/kg per day when the patient could tolerate oral medications, then tapered to 0.1 mg/kg per day

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ISSN: 1056-9103/06/1405-0283

TABLE 1. Patients Colonized or Infected With *Aspergillus* According to Year and Disease State

Disease State	1999 (n = 25)	2000 (n = 38)	2001 (n = 40)
Colonization	4 (16)	4 (11)	11 (28)
Tracheobronchitis	3 (12)	6 (16)	4 (10)
Invasive (pneumonia)	2 (8)	4 (11)	1 (3)
Total	9 (36)	14 (37)	16 (40)

Data are expressed as number (%).

over 6 months), azathioprine 2 mg/kg per day, and cyclosporine A, dosed for levels between 200 and 250 ng/mL in the early postoperative period. Acute rejection episodes were treated with intravenous methylprednisolone 1 g/d for 3 days followed by prednisone 20 mg/kg per day for 1 week, with subsequent taper to the prerejection maintenance dose. Tacrolimus and mycophenolate mofetil were used in cases of cyclosporine intolerance or steroid-refractory rejection.

Prophylaxis for bacterial infection consisted of vancomycin and a β -lactam antibiotic (cefuroxime or ceftazidime intravenously) for 48 to 72 hours posttransplant. Patients with a β -lactam allergy received either aztreonam or a fluoroquinolone in addition to vancomycin. Antibiotics were continued and adjusted based on positive culture results from donor and recipient bronchi at the time of transplantation or for clinical suspicion of infection. Ganciclovir was administered for 90 days postoperatively for cytomegalovirus (CMV) seropositivity in either the donor or recipient, whereas acyclovir was used when both the donor and recipient were CMV seronegative.

Antifungal prophylaxis was not routinely given before May 1999, at which point itraconazole capsules, at a dose of 200 mg/d, were prescribed for a 3-month course to all patients. Serum levels were not monitored although cyclosporine and tacrolimus were adjusted to maintain therapeutic concentrations. Acid suppression therapy was also used in most of the patients, typically using a histamine H₂ receptor antagonist. Aerosolized amphotericin B deoxycholate, 2 mg TID for 3 to 4 weeks, was administered in addition to prophylactic itraconazole to patients receiving transplants from September 2000 forward. Patients with documented *Aspergillus* tracheobronchitis were treated by increasing the dose of itraconazole to 200 mg orally BID. Invasive aspergillosis was treated with intravenous amphotericin B deoxycholate at a dose of 1.0 to 1.5 mg/kg per day, or, in those intolerant to conventional amphotericin, with a lipid formulation of amphotericin B at 4 to 5 mg/kg per day.

Surveillance bronchoscopy was performed at 3 and 6 weeks after transplantation, as well as at 3, 6, and 12 months after transplantation. Additional bronchoscopies were performed as indicated, for example to investigate pulmonary symptoms or a decline in pulmonary function. Bronchoalveolar lavage fluid was sent for fungal smears and cultures, and transbronchial biopsy specimens were cultured for fungi and examined for hyphal elements. Routine pretransplant sputum cultures or bronchoscopies were not performed unless clinically indicated.

The means of continuous variables were compared using the Student *t* test, whereas categorical variables were evaluated with χ^2 and Fisher exact tests. Multivariate analysis was performed on statistically significant ($P < 0.05$) variables discovered on univariate analysis coupled with variables historically associated with *Aspergillus* infection using logistic regression. Calculations were performed using SPSS 10.0 for Windows (SPSS Inc, Chicago, IL; 1989–1999).

RESULTS

One hundred and three primary lung transplants were included in our study, with 17 sequential double lung and the remainder single lung transplants. Two patients were excluded because of death within 5 days of transplantation, both due to primary graft failure with reperfusion injury. Sixty-six of the recipients were women, and the mean age at time of transplantation was 53 ± 8 years. The primary indication for transplantation was emphysema, including that due to α_1 -antitrypsin deficiency.

There were a total of 39 patients who had *Aspergillus* species isolated within 60 days postoperatively, sometimes on more than 1 occasion. These included 19 patients who were colonized with the organism and 20 with infection due to *Aspergillus* species (13 TB and 7 IA). The number of patients with colonization, TB, or IA according to the year of transplantation is delineated in Table 1. Overall, the percentage of patients colonized or infected with *Aspergillus* was between 36% and 40%. One half of all infections due to *Aspergillus* species were identified during 2000, including 6 (46%) of 13 TB cases and 4 (57%) of 7 invasive pneumonias. Although there was a trend toward greater risk of TB and IA in 2000 compared with the other years studied, it did not reach statistical significance. Conversely, there was a greater incidence of colonization with *Aspergillus* in 2001 (28%) compared with the prior 2 years, particularly 2000 (11%), although this difference was not statistically significant.

Table 2 lists the disease state according to the *Aspergillus* species cultured. There were a total of 41 unique *Aspergillus* isolates recovered with *Aspergillus fumigatus*

TABLE 2. Colonization or Infection According to *Aspergillus* Species

Species	Colonization (n = 19)	TB*† (n = 13)	IA* (n = 7)	Total
<i>A. fumigatus</i>	6	5	6	17
<i>Aspergillus niger</i>	5	4	1	10
<i>Aspergillus flavus</i>	3	5	0	8
<i>Aspergillus terreus</i>	1	0	1	2
Other <i>Aspergillus</i> species	4	0	0	4

*Some cases have more than 1 species cultured.

†One case identified by histopathology only.

TABLE 3. Characteristics of Infected Versus Uninfected Patients

Variable	Infected (n = 20)	Uninfected (n = 83)	P
Age, mean $\pm$ SD (y)	53.3 $\pm$ 8.5	52.7 $\pm$ 8.4	NS
Male sex, n (%)	11 (55)	38 (46)	NS
Underlying diagnosis, n (%)			
COPD	16 (80)	67 (81)	NS
Cystic fibrosis	1 (5)	4 (5)	NS
Idiopathic pulmonary fibrosis	0	5 (6)	NS
Sarcoidosis	1	1 (1)	NS
Pulmonary hypertension	1	1	NS
Bronchiolitis obliterans	0	2 (2)	NS
Hypersensitivity pneumonitis	1	0	NS
Other*	0	3 (4)	NS
Unilateral transplant	16 (80)	70 (84)	NS
Aspergillus colonization	4 (20) [†]	19 (23)	NS
Growth of any organism from recipient lung cultures performed at time of transplantation	9 (47)	17 (24) [‡]	0.051
Non-Aspergillus pulmonary infection within 60 days posttransplantation	6 (30)	26 (31)	NS
CMV Infection within 60 days posttransplantation [§]	2 (10)	7 (8)	NS
Rejection therapy	10 (50)	43 (52)	NS
Prophylaxis			
Itraconazole	16 (80)	66 (80)	NS
Aerosolized amphotericin	7 (35)	28 (34)	NS
Length of stay, mean $\pm$ SD (d)	18.8 $\pm$ 33.7	15.5 $\pm$ 18.6	NS
Mortality at 60 days	2 (10)	9 (11)	NS
Mortality to date	11 (55)	30 (36)	NS

(median follow-up, 575 days; range, 8–1457 days)

*One patient each with pulmonary hemosiderosis, eosinophilic granuloma, and Swyer-James syndrome.

[†]“Colonization” in this group refers to isolation of *Aspergillus* before diagnosis of infection.[‡]The sample number of population is 71 because recipient lung cultures were not available for all patients.[§]Includes CMV diagnosed by viral culture, antigen testing, polymerase chain reaction, or histological evaluation.

COPD indicates chronic obstructive pulmonary disease.

being identified most frequently. *Aspergillus fumigatus* accounted for most (6/8 or 75%) of the IA cases and, when isolated, was less likely to be colonizing the respiratory tract than other species of *Aspergillus*. In addition, the 2 deaths which occurred within 60 days postoperatively occurred in patients infected with *A. fumigatus*. Regardless of the isolate involved, most patients survived their infection, with 4 deaths directly attributable to aspergillosis (20% mortality among infected patients), followed up to 2 years posttransplantation.

An analysis was undertaken to identify risk factors for *Aspergillus* infection (Table 3). There was no difference in age, sex, or underlying diagnosis leading to transplantation between patients infected with *Aspergillus* and uninfected individuals. Immunosuppressive regimens were similar for both groups, including treatment of acute rejection episodes within 60 days posttransplantation. Technical variables of the operation such as donor lung oxygenation, ischemic time, and total operative duration did not differ between those with and without aspergillosis (data not shown). Infections with other organisms in the early postoperative period, including CMV, occurred in 30% to 40% of all patients independent of infection with *Aspergillus* species. Prophylactic measures

against bacterial, viral, and fungal pathogens were also similar between the 2 groups.

The presence of *Aspergillus* species at the time of transplantation was not associated with an increased risk of *Aspergillus* infection. Among 8 patients who grew *Aspergillus* from bronchoscopic cultures from either the donor or recipient lungs at the time of transplant, only one later developed *Aspergillus* tracheobronchitis. It should be noted, however, that in these patients, the oral itraconazole dose was increased from once to twice daily in response to the isolation of *Aspergillus*. Furthermore, surveillance cultures were not necessarily sensitive to detecting *Aspergillus* infection before clinical manifestations; only 4 of the 20 patients with aspergillosis after transplantation had an *Aspergillus* isolate before the diagnosis of active infection. However, positivity of recipient lung cultures for any pathogen at the time of transplantation was associated with an increased risk of subsequent *Aspergillus* infection. Bronchoalveolar lavage cultures yielded growth in 9 (47%) of 20 of the *Aspergillus* infected versus 17 (24%) of 71 uninfected patients, which was significant with a $P = 0.051$. These cultures most frequently grew bacterial organisms,

such as *Staphylococcus* or *Pseudomonas* species, rather than fungal isolates.

A higher rate of *Aspergillus* infections occurred in the third quarter of 2000 as compared with other periods. Among patients transplanted during this time, corresponding to July 2000 through September 2000, there were a total of 7 *Aspergillus* infections. This accounted for 35% of all infections during the study period ($P = 0.021$ for this quarter in comparison with infections occurring outside this period). These included 3 cases of IA (43% of the total invasive cases) and 4 TB (31% of the total TB cases), with 2 patients dying in the early postoperative period as a direct consequence of their fungal infection. A subgroup analysis of the patients transplanted during this period did not reveal any significant differences compared with the remaining lung transplant recipients.

Multivariate analysis using logistic regression was performed to determine the significance of transplantation date and recipient culture results as independent predictors of disease due to *Aspergillus*. Controlling for prior *Aspergillus* colonization, CMV infection, single lung transplantation, and acute rejection therapy as historical determinants of *Aspergillus* infection risk, only transplantation during the third quarter of 2000 remained as a significant predictor of aspergillosis in our cohort ($P = 0.026$).

Antifungal prophylaxis was initiated in the immediate postoperative period in greater than 80% of our patients. As previously stated, this consisted of either oral itraconazole, aerosolized amphotericin B deoxycholate, or both. There was no difference in the rate of colonization or infection in those who received antifungal prophylaxis, regardless of the drug(s) used (Table 3). Although the mortality rates at a median follow-up of 575 days were not significantly different among those infected with *Aspergillus* and those uninfected, there was a trend toward increased mortality among patients who had experienced *Aspergillus* infection (55% vs. 36%, Table 3).

DISCUSSION

Aspergillus infection among lung transplant recipients can result in one of several clinical illnesses. Manifestations include endobronchial infection, particularly at the anastomotic site, as well as invasive pulmonary disease with or without extrapulmonary dissemination.^{3,9–11} Allergic bronchopulmonary aspergillosis and isolated infection outside of the lungs have also been reported.^{12,13} Isolation of the organism from the respiratory tract, however, does not always signify disease, as asymptomatic colonization is reported in 10% to 85% of patients posttransplantation.^{1,14,15} Thus, attempts have been made to identify patients predisposed to infection after lung transplantation, but such risk factors are poorly understood.

Previous work has shown an association of colonization with *Aspergillus* and subsequent infection.¹⁶ Patients with cystic fibrosis, however, who are more frequently colonized pretransplantation than other lung transplant recipients, do not appear to be at increased risk for invasive aspergillosis, although early anastomotic infection may be

more common in this subgroup.^{17–19} Single lung recipients may also have increased risk as compared with double lung recipients.²⁰ Cytomegalovirus infection has been shown to be associated with aspergillosis, perhaps by acting as an immunomodulator,²¹ as has allograft rejection with augmented immunosuppression.²² Finally, as previously stated, environmental factors such as hospital construction have been associated with *Aspergillus* outbreaks in other immunocompromised populations.

The present study quantitates the risk of *Aspergillus* infection in a large group of lung transplant recipients and attempts to identify risk factors for aspergillosis in the early postoperative period. The time frame encompassing 60 days posttransplantation was chosen for several reasons. First, in the absence of rejection therapy, it generally corresponds to the period of maximal immunosuppression. Second, the healing anastomotic site may be most vulnerable to infection at this time due to local tissue injury and operative ischemia.⁸ Lastly, antifungal prophylactic medications are commonly used during this period, although their efficacy is uncertain in this population. We could not identify any variables such as pretransplant *Aspergillus* colonization, type of lung transplant, CMV infection, or treatment of rejection as being associated with *Aspergillus* infection after lung transplantation. However, our decision to study the early posttransplant period may have influenced some of these findings. Early CMV infection, for example, may have been limited by antiviral prophylaxis during this time. Furthermore, the impact of these variables on cases of aspergillosis beyond 60 days posttransplantation was not investigated. It is also possible that clinically inapparent differences in the level of immunosuppression of particular patients may have conferred an increased risk for aspergillosis. In this regard, there is an interest in developing assays which can accurately reflect lymphocyte function and stratify risk for opportunistic complications,^{23,24} but it seems unlikely that there would have been such a change in the third quarter of 2000 to account for the increased incidence of aspergillosis in our patient population.

We did observe a significant increase in *Aspergillus* infection among those recipients with lung cultures positive for any organism pretransplantation. As most of these cultures prompted extended antibiotic therapy, we postulate that broad-spectrum antimicrobial use may have contributed to alteration of the patients' endogenous flora, facilitating infection by *Aspergillus* species. Although growth of microorganisms from recipient lung BAL was associated with increased antibiotic use, there was no significant association between antibiotic duration, specific antibiotic class, or number of antimicrobial classes used and risk of aspergillosis (data not shown). Alternatively, an immunodulatory effect of the cultured organisms could influence the risk of *Aspergillus* infection. This seems less likely, however, as those with clinical evidence of pulmonary infection, including that due to CMV, did not have increased rates of *Aspergillus* tracheobronchitis or invasive disease. Nonetheless, it is possible that the recipient cultures reflect some anatomic or physiological difference in the culture-positive host which influences the risk of subsequent *Aspergillus* infection. To clarify the importance of recipient lung BAL

cultures as a predictor of fungal diseases, further investigation in a larger patient population may be warranted.

Mehrad et al¹¹ evaluated 133 cases of consecutive lung transplant recipients in an earlier period at our institution to define the incidence and natural history of *Aspergillus* infection. They found airway colonization due to *Aspergillus* in 29% of patients, with tracheobronchitis and invasive pneumonia in 5% and 8%, respectively.¹¹ Although these rates were comparable with those found in other series at the time, routine antifungal prophylaxis was instituted after the study in an effort to lessen the impact of fungal disease on subsequent lung transplant recipients. Although the rate of colonization fell to 17.5% in our series, tracheobronchitis and invasive aspergillosis occurred in 12.6% and 6.8%, respectively, with all infections occurring in patients who had received antifungal prophylaxis.

The fact that our study did not show a benefit from antifungal prophylaxis is of interest and is likely multifactorial. Although several small retrospective studies have demonstrated efficacy of itraconazole in limiting *Aspergillus* infections, prospective data from larger trials are limited, with conflicting results regarding its prophylactic benefit.^{25–27} As an alternative to universal antifungal prophylaxis, preemptive treatment for those with *Aspergillus* colonization is often practiced. However, because large randomized trials of preventive antifungal use after lung transplant are lacking, prophylactic and preemptive strategies are controversial and approaches vary at different transplant centers.²⁸ The low predictive value of *Aspergillus* colonization of subsequent infection and the low sensitivity of surveillance cultures demonstrated in the present study underscores the difficulty with the preemptive treatment approach. In our population, any potential benefit from itraconazole use was likely tempered by the erratic absorption of the capsule formulation, compounded by gastric acid suppression therapy used in most of our transplant recipients. Furthermore, the optimal prophylactic dose of itraconazole remains unclear, and serum levels were not monitored routinely in our patients. Efforts to increase itraconazole absorption such as limiting acid suppression therapy and/or concomitant cola administration²⁹ coupled with therapeutic drug monitoring may have improved the efficacy of prophylaxis. Alternatively, use of the more bioavailable itraconazole oral solution may be the preferred option.³⁰ The impact of newer antifungal agents such as voriconazole and caspofungin is as yet unknown with respect to prophylaxis against fungal infection in lung transplantation.³¹

Aerosolized amphotericin B is another option for antifungal prophylaxis after lung transplant, but there is limited evidence to support its use among solid organ transplant recipients. Although data from several small studies are encouraging, the dosing interval and duration for optimal benefit is unknown.^{32,33} Side effects, principally cough, wheezing, and nausea, occur in almost one half of patients treated with the deoxycholate formulation, with intolerance leading to discontinuation of the drug in up to 25% of patients. Lipid formulations of the drug may be as efficacious and better tolerated, with 2% breakthrough infection rate and 5.9% discontinuation rate observed in a randomized trial comparing amphotericin B lipid complex with conventional amphotericin

in 100 lung transplant recipients.^{34,35} Finally, the beneficial effect of combinations of prophylactic medications has not been experimentally validated.

The reason for the increased rate of *Aspergillus* infection occurring in our study during the third quarter of 2000 is unclear, although environmental factors may have played a part. Construction was ongoing in the hospital during this period, although not in areas immediately adjacent to the operating rooms, recovery areas, or inpatient wards, and patients did not pass through construction areas on the way to the Radiology Department or outpatient clinic appointments. Furthermore, no hospitalwide increase in *Aspergillus* infection was noted nor was there an increase in rates of aspergillosis among other solid organ or bone marrow transplant recipients during this time. Whereas a laminar airflow system is used in the operating areas, no additional air processing methods (ie, High Efficiency Particulate Air filters) are used in other patient care areas for patients undergoing lung transplantation. Such strategies have proven helpful in bone marrow transplant units to reduce the environmental burden of *Aspergillus* conidia in the hospital, although waterborne or outpatient acquisition of this ubiquitous pathogen may limit the impact of these measures.^{6,36–38}

In summary, *Aspergillus* colonization and infection is a frequent occurrence in the early postoperative period after lung transplantation, occurring in 36% to 40% of patients. We reviewed the risk of *Aspergillus* infection and factors associated with early postoperative aspergillosis among 103 lung transplant recipients. We found an increased prevalence of infection only in association with a specific period of transplantation, suggesting the importance of environmental exposure as a significant risk of *Aspergillus* infection in the patient population. Because our study is limited by its retrospective design and power to define significant risk given the low occurrence of clinically evident infection, further study in this area is clearly warranted. Risk stratification coupled with improved diagnostic modalities may allow more judicious targeting of antifungal prophylaxis or preemptive therapy.

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