

# The Impact of Culture Isolation of *Aspergillus* Species: A Hospital-Based Survey of Aspergillosis

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The term “aspergillosis” comprises several categories of infection: invasive aspergillosis; chronic necrotizing aspergillosis; aspergilloma, or fungus ball; and allergic bronchopulmonary aspergillosis. In 24 medical centers, we examined the impact of a culture positive for *Aspergillus* species on the diagnosis, risk factors, management, and outcome associated with these diseases. Most *Aspergillus* culture isolates from nonsterile body sites do not represent disease. However, for high-risk patients, such as allogeneic bone marrow transplant recipients (60%), persons with hematologic cancer (50%), and those with signs of neutropenia (60%) or malnutrition (30%), a positive culture result is associated with invasive disease. When such risk factors as human immunodeficiency virus infection (20%), solid-organ transplantation (20%), corticosteroid use (20%), or an underlying pulmonary disease (10%) are associated with a positive culture result, clinical judgment and better diagnostic tests are necessary. The management of invasive aspergillosis remains suboptimal: only 38% of patients are alive 3 months after diagnosis. Chronic necrotizing aspergillosis, aspergilloma, and allergic bronchopulmonary aspergillosis have variable management strategies and better short-term outcomes.

*Aspergillus* species are saprophytic, thermotolerant fungi that survive and grow on organic debris and that aerosolize conidia, which humans inhale at the rate of hundreds per day without experiencing complications [1].

However, 19 *Aspergillus* species can produce a spectrum of diseases, including allergic bronchopulmonary aspergillosis (ABPA), aspergilloma, chronic necrotizing aspergillosis, and life-threatening invasive aspergillosis (IA) [2–4].

Epidemiological studies of aspergillosis have focused on increases in the number of cases of such disease at single institutions. Despite the use of molecular techniques to identify specific strains and to link environmental and geographically diverse strains with infection [5–9], nosocomial assessments of *Aspergillus* colonization versus infection remain imprecise. For instance, at one institution, air sampling identified potential environmental exposures for high-risk patients with infection [10]; however, in another study, concentrations of airborne *Aspergillus* conidia did not correlate with disease [1]. Although environmental exposure may play a role in the development of IA, variability between

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institutional environments suggests that a multicenter study is needed to determine the true magnitude of aspergillosis.

We examined the spectrum of aspergillosis at 24 medical centers by assessing cultures that were positive for *Aspergillus* species; such assessment made the study less susceptible to institutional biases and local variances in management. The survey was performed during a period when there was a marked increase in the incidence of aspergillosis among immunocompromised patients [11–13]. A culture positive for *Aspergillus* species was required for patient entry into the study. This strategy allowed for nonbiased, comprehensive selection of patients at risk for both fungal colonization and fungal infection.

## METHODS

“Case patients” were defined as subjects with a culture yielding *Aspergillus* species who were identified by a search of microbiology laboratory logs for the period from 1 January 1995 through 31 December 1995. The Aspergillosis Case Surveillance Form was created for the collection of the following data: sites of infection and species identification; age, sex, race, and hospital location of the patient; presence of other concomitant infectious diseases; underlying medical conditions; use of immunosuppressive, immunostimulant, or cytotoxic medications; clinical condition (e.g., disease, colonization, or contamination) and classification of disease as belonging to 1 of 4 categories (IA, chronic necrotizing aspergillosis, aspergilloma, and ABPA); radiographic evidence of disease; treatments initiated because of a positive *Aspergillus* culture result; and survival at 3 months after diagnosis.

The clinical condition and disease classification for each case were determined by the principal investigator at each site. The principal investigators were members of the Mycoses Study Group. After chart review, the principal investigator assigned each patient to 1 of 3 groups, according to whether the patient’s clinical condition involved infection, colonization, or contamination of culture plates. For 3-month-survival analysis, the principal investigator assessed whether death was due to aspergillosis, an underlying disease with or without aspergillosis, or an unknown cause. For standardization of diagnoses among the medical centers, cases of IA were classified by the principal investigator as “definite,” “probable,” or “possible,” on the basis of modified criteria from previous Mycoses Study Group studies (table 1) [14, 15]. For analysis, these 3 classifications were collectively considered to be IA.

Colonized patients had clinical or radiographic evidence that was consistent with the possibility that *Aspergillus* species were part of their flora but that, in the opinion of the principal investigator, caused no clinical features of disease. Contamination was considered to be the classification when isolation of the mold had neither an apparent connection with the clin-

ical condition nor relevance to the patient’s care. Identification of chronic necrotizing aspergillosis, aspergilloma, or ABPA was made by the principal investigator at each site and was based on well-described clinical criteria [16–19]. Compilation of figures and statistical analyses of data were performed at the Mycoses Study Group Biostatistics Unit at the University of Alabama at Birmingham. Descriptive statistics (including means and standard errors) summarized continuous measures; binomial proportions summarized dichotomous data. The association between *Aspergillus* species and the disease category was evaluated by  $\chi^2$  analysis. A stepwise logistic regression model was used to examine the association of underlying risk factors with invasive disease.

## RESULTS

In 1995, the 24 medical centers reported a total of 1477 separate *Aspergillus*-positive cultures for 1209 patients who were randomly selected from a pool of 1856 patients. Seven centers had  $\geq 10$  cases of IA. Conversely, 4 centers had no cases of IA identified by culture. If the medical centers were grouped on the basis of 4 geographic sections of North America (East, Southeast, Midwest, and West), there was a similar average distribution of IA cases per center in each area. Chronic necrotizing aspergillosis was diagnosed at 10 of the 25 centers. Thirteen centers had  $\geq 1$  case of aspergilloma, and 5 of these centers reported  $\geq 3$  cases. A significant medical center bias for ABPA was observed, with 2 medical centers (the University of Michigan and Veterans Affairs Medical Center at Ann Arbor, Michigan, and the University of Montreal) reporting 80% of cases. Demographic features of the patients are summarized in table 2.

IA was most often caused by *Aspergillus fumigatus* (table 3). There was a significant difference between *Aspergillus* species, with respect to their disease distribution ( $P = .001$ ). When disease categories were identified, *Aspergillus terreus* (8 of 8 positive culture results) was always isolated from patients with IA, and *Aspergillus flavus* (41 [83%] of 49 positive culture results) was predominantly associated with IA. For patients with chronic necrotizing aspergillosis, aspergilloma, and ABPA, the majority of cultures yielded *A. fumigatus*.

*Aspergillus* species were isolated from a variety of body sites. The majority of isolates (81%) recovered from patients with either infection or colonization were from nonsterile respiratory secretions, such as sputum samples (733 of 1477 positive culture results) and bronchoalveolar lavage specimens (344 of 1477 positive culture results); however, they occasionally were from potentially sterile sites (e.g., tissue biopsy specimens [26 of 1477 positive culture results]). Other body sites included sinus, skin, bone, pleura, prostate, and liver. There were 15 positive blood culture results and 7 positive brain culture results, but there

**Table 1. Criteria for defining cases of invasive aspergillosis.**

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Classification, criteria
Definite
A. Positive result of histologic testing and positive result of culture of a specimen from the same site <i>or</i>
B. Negative results of histologic testing or positive results of culture of a specimen obtained from a sterile site by use of invasive techniques
Probable
A. Appropriate host (as defined by item 1, 2, 3, or 4 below) and a procedure to make definite diagnosis contraindicated
1. Neutropenia (absolute neutrophil count, <500 neutrophils/mm <sup>3</sup> )
2. Use of cytotoxic agent(s)
3. Glucocorticoid therapy (prednisone or equivalent, >20 mg/day)
4. Congenital or acquired immunodeficiency
B. Either 2 positive results of sputum specimen cultures, 2 positive results of throat specimen cultures, 1 positive result of bronchoscopy specimen culture or smear <i>or</i>
C. Meets criteria for definite invasive aspergillosis in another organ system
Possible
A. Patient received cytotoxic therapy for leukemia <i>and</i>
B. Procedure to make a definite diagnosis either was contraindicated or was attempted but resulted in findings negative for the presence of the pathogen <i>and</i>
C. Presence of $\geq 5$ of the following criteria
1. Temperature $\geq 100^\circ\text{F}$ ( $\geq 38^\circ\text{C}$ ) at admission
2. Neutropenia (absolute neutrophil count, <500 neutrophils/mm <sup>3</sup> ) for >30 days
3. $\geq 2$ Febrile episodes (temperature, $\geq 100^\circ\text{F}$ or $\geq 38^\circ\text{C}$ ) of unknown source
4. Febrile episodes of unknown source for $\geq 14$ days
5. Patient is febrile for $\geq 19$ days while receiving antibacterials
6. Rales without volume overload
7. Observation of nasal eschar, ulcer, or discharge with epistaxis and sinus tenderness
8. Pleuritic chest pain
9. Chest infiltrate first seen radiologically after hospital day 14
10. Pulmonary infiltrate in >1 lobe
11. Chest radiograph showing nodules or cavities [14]

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were no positive CSF culture results. Of the patients with IA, 61% had only 1 positive culture result and 18% had  $\geq 3$  positive culture results. For patients with other disease categories, approximately one-half of the patients had  $\geq 1$  positive culture result. Two-thirds of the patients were located on the inpatient hospital services, including the medicine (37%), intensive care unit (14%), surgery (8%), and oncology (5%) services.

On the basis of the clinical criteria for definite, probable, and possible infections, in addition to clinical judgment and standard descriptions for the other 3 categories, the 1209 cases were reduced to 245 cases of clinical disease. Twelve percent of patients with cultures that were positive for *Aspergillus* met criteria for IA, and 97 cases belonged to the other 3 disease categories (table 4). Of the 148 cases of IA, 90 (61%) were classified as definite, 49 (33%) as probable, and 9 (6%) as possible. Advanced radiography was used to establish a diagnosis of IA in fewer than one-half of the cases (specifically, for the diagnosis of 48 cases [30%], a CT scan was obtained; for

3 cases [ $<1\%$ ], an MRI scan was obtained; and for 6 cases [4%], both were obtained).

Underlying diseases or characteristics of patients who had *Aspergillus* isolates are shown in table 5. Patients who had  $\geq 1$  risk factor were included in each appropriate risk category. From these data on patients with a positive culture result and clinical classification of disease, a prediction was made of the risk for IA in persons with underlying disease. The risk factors were arbitrarily grouped into 3 categories for presentation: high, intermediate, or low risk for IA (table 6). Among high-risk patients, a positive culture result was associated with IA in 50%–65% of cases. Among patients with an intermediate risk, 8%–28% of patients with positive culture results had IA. Patients in the low-risk category rarely had IA. If further analysis showed that the cultures were indicative of colonization or infection, and if cultures with contamination or of unknown significance were eliminated from the denominator value (the number of cases for which *Aspergillus* species were isolated),

**Table 2. Demographic features of all patients from whom an *Aspergillus* isolate was recovered.**

Demographic feature	No. (%) of patients (n = 1209)
Sex	
Male	704 (58)
Female	505 (42)
Race	
White	858 (71)
Black	194 (16)
Latino	49 (4)
Asian	17 (1)
American Indian/Alaskan	7 (1)
Unknown	84 (7)
Age, mean years ± SEM	48.9 ± 0.6

the risk rates in the high-risk and intermediate-risk groups were even higher, with risks of IA of 70%–80% and 20%–50%, respectively. It should be noted that, for some patients, underlying disease risk may overlap with other risk categories (i.e., steroid use and bone marrow transplantation).

When a multivariate logistic regression model was used to evaluate the association between the risk factors shown in table 6 and both the presence of IA and a positive culture result, underlying diseases or characteristics, such as allogeneic bone marrow transplants, hematologic cancer, HIV infection, and solid-organ transplants, along with the clinical conditions of neutropenia and malnutrition, were associated with IA ( $P < .001$ ). In contrast, for patients with cystic fibrosis, a positive culture result was associated with absence of IA ( $P < .001$ ).

Coinfections were a potential confounding risk factor for the survival of patients with IA. Of the 148 patients with IA, 44 (30%) had a bacterial infection, 30 (20%) had viral infection

diagnosed, and 19 (13%) were found to have another fungal infection. However, there were no differences between patients with IA who did or did not have a concomitant infection during their 3-month survival.

One-third of the patients with chronic necrotizing aspergillosis had a known underlying pulmonary condition and/or had been receiving corticosteroids. Patients with aspergilloma generally had an underlying pulmonary condition (~60%) and/or had previously undergone surgery (12%). Aspergillomas were also observed in 9 patients with bone marrow transplants, solid-organ transplants, or hematologic malignancies. Patients with ABPA also had other risk factors, including corticosteroid use (26%) and/or evidence of an underlying pulmonary disease, such as cystic fibrosis (37%).

Predicting the outcome of patients with IA is complex because of underlying diseases plus difficulties associated with diagnosis and treatment. We measured an unequivocal outcome endpoint of survival at 3 months (table 7). Colonization with *Aspergillus* species was a marker for reduced short-term survival, in that 12% of colonized patients died within 3 months of receiving a positive culture result. Despite receiving treatment with amphotericin B, more than one-half of the patients with IA were dead within 3 months of receiving a positive culture result. Furthermore, when this outcome was specifically analyzed for the more subjective measurement of direct impact of infection, the principal investigators judged that death was directly attributable to aspergillosis in 38% of the patients who received amphotericin B. Itraconazole was used less frequently for treatment than was amphotericin B, but it was associated with a 21% rate of death due to aspergillosis. When patients who were treated with amphotericin B alone were considered separately from those receiving both amphotericin B and itraconazole, the death rate associated with aspergillosis was found to be 36.6% versus 8.3%, respectively.

There were no significant differences in survival associated

**Table 3. Disease-producing *Aspergillus* species, according to positive culture results.**

<i>Aspergillus</i> species	No. (%) of positive culture results, according to clinical condition					
	Invasive disease (n = 256)	Chronic necrotizing aspergillosis (n = 41)	Aspergilloma (n = 83)	ABPA (n = 87)	Colonization (n = 735)	Contamination (n = 275)
<i>A. flavus</i>	41 (16)	1 (2)	2 (2)	5 (6)	66 (9)	29 (10)
<i>A. fumigatus</i>	171 (67)	33 (80)	57 (69)	80 (92)	465 (63)	102 (37)
<i>A. nidulans</i>	2 (1)	0 (0)	0 (0)	0 (0)	5 (1)	2 (1)
<i>A. niger</i>	14 (5)	4 (10)	11 (13)	0 (0)	101 (14)	66 (24)
<i>A. terreus</i>	8 (3)	0 (0)	0 (0)	0 (0)	8 (1)	1 (1)
Other	2 (1)	3 (8)	4 (5)	0 (0)	28 (4)	17 (6)
Not identified	18 (7)	0 (0)	9 (11)	2 (2)	62 (8)	58 (21)

**NOTE.** ABPA, allergic bronchopulmonary aspergillosis.

**Table 4. Types and numbers of cases of clinical disease for which a culture was positive for *Aspergillus* species.**

Clinical disease	No. (%) of cases (n = 1209)
Invasive disease	148 (12)
Chronic necrotizing aspergillosis	19 (2)
Aspergilloma	43 (4)
Allergic bronchopulmonary aspergillosis	35 (3)

with amphotericin B or itraconazole treatment administered to those with high-risk vs. intermediate-risk underlying diseases. Twenty-two patients received lipid formulations of amphotericin B, and, when they were compared with patients who received amphotericin B deoxycholate, there was no difference in the percentage of survivors between the 2 groups. The 5 medical centers with the most cases of IA were compared with regard to the percentage of patients who were dead at 3 months as a result of aspergillosis, and no differences were found among these institutions.

For the other categories of *Aspergillus* infection, drug management was recorded. For chronic necrotizing aspergillosis, 5 patients received amphotericin B, 11 patients received itraconazole, and 3 patients were not treated. Three patients (16%) with chronic necrotizing aspergillosis died of their infection, but 63% were alive at 3 months, regardless of whether they had discontinued or were still receiving medications; the other patients were lost to follow-up. Of the 43 patients with aspergilloma, only 1 (2%) had the lesion surgically removed. Nine patients (21%) received treatment with amphotericin B, 18 (42%) received itraconazole, 3 (7%) received fluconazole, and others received no treatment. Analysis of the outcome associated with aspergilloma showed that 35 patients (81%) were alive at 3 months, with half of these patients still receiving antifungal medications; only 1 patient died of this infection. Of the patients with ABPA, 8 (23%) of 35 received antifungal agents (2 received amphotericin B and 6 received itraconazole), and none died.

## DISCUSSION

*Aspergillus* species, prevalent airborne fungal pathogens, have caused an increased number of reported cases of infection during the past decade [11–13, 20]. Davis et al. [21], using the Health Care Cost and Utilization Project and the National Inpatient Sample from the Agency for Health Care Research and Quality, attempted to gauge the burden of aspergillosis. They found that, from 1993 through 1996, there was an increase in the rate of aspergillosis-related hospitalizations. Furthermore, hospitalizations for aspergillosis cost substantially more than

non-aspergillosis-related hospitalizations and were associated with lengthy hospital stays and a high mortality rate [21].

In our survey, several demographic features associated with the isolation of *Aspergillus* species should be emphasized. Males are slightly more likely to have cultures that are positive for *Aspergillus* species, and this predominance among males occurred for patients with all disease categories except ABPA. The slight predominance among males is similar to that for cryptococcosis among non-HIV-infected patients [22]. Although racial bias has been well described in cases of mycoses, such as coccidioidomycosis, none was observed for aspergillosis. The typical patient from whom an *Aspergillus* species is isolated is ~50 years of age; although outbreaks of aspergillosis occur in neonatal units, and although the disease occurs in pediatric patients with cancer and in bone marrow transplant recipients [23, 24], these groups were not represented.

*A. fumigatus* was the most frequently isolated species. *A. flavus* accounted for almost one-fifth of the strains causing IA, and both it and *A. terreus* were statistically associated with IA. The polyene-resistant strain *A. terreus* [25] comprised only 3%

**Table 5. Underlying diseases or characteristics among all patients from whom an *Aspergillus* isolate was recovered.**

Underlying disease or characteristic	No. (%) of patients (n = 1209)
Pulmonary disorder	477 (40)
Corticosteroid use	381 (32)
Diabetes mellitus	151 (12)
HIV infection	138 (11)
Cystic fibrosis	127 (11)
Surgery	126 (10)
Solid-organ cancer	124 (10)
Hematologic cancer	106 (9)
Solid-organ transplant	100 (8)
Malnutrition	99 (8)
Neutropenia	61 (5)
Allogeneic transplant	39 (3)
Graft-vs.-host disease	34 (3)
Trauma	24 (2)
Connective tissue disease	28 (2)
Autologous transplant	14 (1)
Chronic granulomatous disease	2 (<1)
None	92 (8)

**NOTE.** These data are for individual cases in which an *Aspergillus* isolate was recovered from  $\geq 1$  culture. The data include patients considered by a medical mycologist/clinician to be colonized or infected or whose cultures were contaminated, without evidence of clinical significance. Patients may be included in  $\geq 1$  category (thus allowing for a total percentage >100%).

**Table 6. Risk of invasive aspergillosis (IA) among patients whose cultures were positive for *Aspergillus* species.**

Risk category, feature	Risk of IA, no. of cases (%) <sup>a</sup>
High	
Allogeneic BMT	25/39 (64)
Neutropenia	39/61 (64)
Hematologic cancer	53/106 (50)
Intermediate	
Autologous BMT	4/14 (28)
Malnutrition	27/99 (27)
Corticosteroids	78/381 (20)
HIV	26/138 (19)
Solid-organ transplant	21/124 (17)
Diabetes	17/151 (11)
Underlying pulmonary disease	45/477 (9)
Solid-organ cancer	10/126 (8)
Low	
Cystic fibrosis	1/127 (0.7)
Connective tissue disease	0/28 (0)

**NOTE.** A case can be included in  $\geq 1$  disease classification. BMT, bone marrow transplant.

<sup>a</sup> Number to the left of the virgule, no. of cases of IA; number to the right of the virgule, no. of cases in which an *Aspergillus* species was isolated.

of isolates in cases of IA, but it was found exclusively in cases of IA. A recent review noted that 10% of cases of IA were caused by this fungus and that the disease progressed rapidly in immunocompromised hosts [26].

The design of our survey allowed us to understand the impact of isolation of *Aspergillus* species by culture of specimens from sterile and nonsterile body sites. More than a dozen blood cultures were positive for *Aspergillus* species. Duthie and Denning proposed criteria for the significance of blood cultures yielding *Aspergillus* species [27], and Kontoyiannis et al. [28] used these criteria to examine the impact of aspergillemia. Most bloodstream isolates of *Aspergillus* species were associated with pseudofungemia or terminal events noted at autopsy; only *A. terreus*, with its ability to produce yeastlike forms in tissue, was a common cause of true aspergillemia [28, 29]. CNS aspergillosis is associated with a high mortality rate [30], and we identified several brain specimens in which *Aspergillus* species were present.

Four disease categories of aspergillosis were analyzed. IA was diagnosed in 12% of patients whose culture results were positive, but it is probable that some cases of IA were missed because culture specimens were not obtained, because radiographs were used for diagnosis, or because only histopathologic findings were positive. In the future, the numbers of identified

cases of IA will likely increase with the development of such tests as PCR [31–33]; serological markers, such as galactomanan [34, 35]; and validation of radiographic methods [36, 37]. The other disease categories for aspergillosis (chronic necrotizing aspergillosis [16, 17], aspergilloma [38], and ABPA [39, 40]) represent a smaller number of cases in comparison with IA, with a bias toward certain medical centers.

Although patients with IA and no apparent underlying disease have rarely been described [41], it is clear that certain risk factors influence the incidence of disease. From the data in table 5, we determined the diseases associated with both isolation of and infection with *Aspergillus* species. Patients may have  $\geq 1$  risk factor for aspergillosis. For instance, corticosteroid use and diabetes may be linked; neutropenia and bone marrow transplantation are linked. The clinical impact of aspergillosis is brought into focus by the culture positivity of specimens obtained from nonsterile sites and by their identification as markers for IA. In a series of cases of IA, the sensitivity of cultures of respiratory tract specimens ranged from 15% to 69% [42–47]. Dummer and Horvath found the sensitivity of positive cultures of bronchoalveolar lavage specimens from cases of IA to be 77% [48]. However, the predictive value of a culture positive for IA may best be evaluated in the context of underlying conditions.

Yu et al. [49] established risk-group profiling as a means of determining the significance of a culture positive for *Aspergillus*. For instance, the predictive value of a culture positive for IA in a group with leukemia/neutropenia was  $>80\%$  [49]. Horvath

**Table 7. Outcome at 3 months for patients who had an *Aspergillus* species isolated.**

Group, characteristic (no. of patients)	Percentage of patients dead at 3 months, according to cause of death		
	Aspergillus	Underlying disease	Other/unknown
Disease classification			
<i>Aspergillus</i> colonization (508)	<1	3	9
IA (148)	40	10	12
Risk			
Allogeneic BMT (39)	39	10	8
Autologous BMT (14)	29	7	0
Neutropenia (61)	34	16	13
Hematologic cancer (106)	27	12	11
Solid-organ cancer (124)	5	3	18
Corticosteroid use (381)	11	7	15
Treatment for IA			
Amphotericin B (95)	38	11	11
Itraconazole (43)	21	7	2

**NOTE.** BMT, bone marrow transplant; IA, invasive aspergillosis.

and Dummer [48], using risk stratification, found that a positive culture result predicted IA in 72% of episodes among patients with hematologic malignancy, granulocytopenia, or bone marrow transplant; in 58% of episodes among those with a solid-organ transplant or corticosteroid use; and in 14% of episodes among those with HIV infection [48]. In our survey, the high-risk group is represented by those with bone marrow malignancies and transplant recipients [50–53]. It is the culmination of risk factors, such as prolonged neutropenia, corticosteroid use, prolonged antibacterial administration, cytotoxic agents, and, in some cases, graft-versus-host disease. The combination of these conditions makes the risk of IA with a positive culture result between 50% and 70%, which is similar to the 72% risk noted at a single institution [48]. Similarly, Wald et al. [52] found that 74% of bone marrow transplantation patients with cultures positive for *Aspergillus* species had documented IA.

Diagnosis of IA on the basis of an *Aspergillus*-positive culture of a specimen obtained from a nonsterile body site remains most difficult for the intermediate-risk group (10%–30%). Classifications such as HIV infection (19%) [54–56], solid-organ transplant (17%) [57–63], and malnutrition (27%) carry a risk of IA when an *Aspergillus* species is isolated from a nonsterile specimen. If patients with contaminated specimens are removed from consideration, percentages for IA increase by ~10% more across each group. In this intermediate-risk group, with specimens from nonsterile body sites, the clinician must aggressively determine, by means of histopathologic tests, radiology, and/or serologic tests, the relevance of an *Aspergillus* isolate with regard to disease [64]. The decision to define the importance of culture may be helped by further stratification. For instance, patients with HIV infection are most at risk for IA when they have prolonged neutropenia, low CD4<sup>+</sup> cell counts, and multiple other opportunistic infections, and/or when they use corticosteroids frequently [54–56]. With HIV infection and multiple other risks for IA, a patient with a positive culture result is at the higher end of the primary risk profile. Solid-organ transplantation may depend on further stratification with consideration of the degree of immunosuppression and technical aspects of the specific transplantation. We observed that only 17% of solid-organ transplant recipients had IA after isolation of *Aspergillus* species; other investigators have reported a higher risk (58%) [48]. Other immediate-risk factors, such as pulmonary disease, diabetes, corticosteroid use, and solid-tumor malignancies, will likely need to be associated with other risks to reach the higher end of the intermediate-risk group percentages for IA.

The occurrence of IA is extremely unusual in cases of cystic fibrosis and connective tissue disease with isolation of *Aspergillus* species. However, these cases may be impacted by *Aspergillus* species under certain circumstances. Patients with cys-

tic fibrosis have a high rate of ABPA. Furthermore, some of these patients undergo lung transplantation, which then elevates the risk of IA [65–67]. Aspergillosis in lung transplants may assume 3 forms—anastomotic infection, tracheobronchitis, and invasive disease [67, 68]; however, it may represent colonization even in the lung transplantation population [69]. Although no IA was associated with a positive culture result among patients with connective tissue disease, it is still prudent to carefully examine a patient in such a group during corticosteroid therapy [70].

Successful management of IA remains a great challenge. Despite the use of polyenes and azoles, the rate of failure of IA treatment remains unacceptably high [71]. Recently, a group of experts reviewed treatment of aspergillosis and summarized a set of therapeutic guidelines [72]. It is clear, from this review and others [73], that there are substantial failures associated with amphotericin B treatment of IA. In our study, amphotericin B failed to directly control IA in 38% of cases, as judged by expert review; this figure is similar to that found in a recent retrospective study (43%) [74]. There was no difference in survival outcome among patients who received standard amphotericin B versus lipid formulations of amphotericin B, but the fact that these preparations are less toxic than amphotericin B [75, 76] may translate into clinical benefits [77].

The interpretation of successes and failures associated with IA management remains difficult, and endpoints are not well defined [78]. There have been several large reviews of outcomes of treatment for aspergillosis, with attempts to define successes and failures [14, 71, 74, 79]. We chose survival at 3 months as an unambiguous endpoint, because most deaths due to IA are observed during this period. It is understood that figures in this analysis represent a combination of factors, including colonization versus infection, prognosis of underlying diseases, treatment doses and toxicities, and location of infections.

Colonization with *Aspergillus* species was a marker for death in 12% of cases and was likely associated with a serious underlying disease. Unfortunately, only 38% of all patients with IA survived longer than 3 months after diagnosis. Furthermore, only 40% of patients who received amphotericin B were alive at 3 months. Although it appears that success rates were better with itraconazole (70%), it is likely that the use of itraconazole selected a less seriously ill population. This hypothesis is supported by the fact that 22% of deaths in the amphotericin B group were not due to aspergillosis, compared with 9% of deaths in the itraconazole group. In another review of outcome, investigators also showed a significant bias for less severely immunosuppressed patients who received itraconazole versus amphotericin B [74]. The successful outcomes associated with itraconazole use in this nonrandomized study should not suggest that itraconazole, rather than amphotericin B, be used as initial therapy for seriously ill patients. In fact, when oral itra-

conazole is used for the management of aspergillosis, blood levels should be checked to ensure drug absorption.

Despite concerns about antagonism of the combination of polyenes and azoles in cases of IA [80], amphotericin B and itraconazole are frequently used together successfully in clinical practice [74, 81]. There is no evidence from this survey that there is a poorer outcome with this combination in treatment. However, the only way to appreciate the full impact of combinations will be to adequately diagnose IA, carefully stage the disease, and study comparative regimens.

Treatment regimens varied for the other 3 categories of aspergillosis disease. This was anticipated because the infections are rare and the treatment guidelines are uncertain. Despite the infrequent use of itraconazole for patients with ABPA (17%), a recent double-blind, placebo-controlled study showed an improvement in the management of ABPA with the use of itraconazole [82]. Surgery is a therapeutic modality for aspergillomas, but only 2% of patients underwent this intervention. Patients with significant pulmonary disease probably could not tolerate surgery or had not had significant hemoptysis. Unlike IA, these 3 categories of infections are generally subacute in presentation and are associated with fewer short-term concerns about mortality.

## THE MYCOSES STUDY GROUP

The medical centers (and individuals) participating in this study were as follows: University of Alabama at Birmingham (P.P.); Vanderbilt Medical Center, Nashville (Stephen Dummer); Duke University Medical Center, Durham, North Carolina (J.R.P. and G.M.C.); University of Texas at San Antonio (Thomas Patterson); Santa Clara Valley Medical Center, San Jose, and Stanford University, Stanford, California (D.A.S.); University of Michigan, Ann Arbor (C.A.K.); Cincinnati Medical Center (Kenneth Skahan); University of Mississippi Medical Center, Jackson (S.W.C. and John Cleary); Oschner Clinic, New Orleans (Ken Pankey); Infectious Disease Associates of Kansas City (David McKinsey); Wayne State University and Harper Hospital, Detroit (P. H. Chandrasekar); Oklahoma Health Science Center (Ronald Greenfield); Albert Einstein University, Bronx, New York (David Stein); Methodist Hospital, University of Tennessee, Memphis (Dan Lancaster); University of Pennsylvania, Philadelphia (Mindy Schuster); University of Montreal (L.d.R., Michel Laverdiere, Gregoire Noel, Claude Lemieux, and Benoit Thivierge); Moffitt Cancer Center, Tampa, Florida (J.W.H.); Case Western Reserve University, Cleveland (Robert Salata); Walter Reed Army Hospital (Duane Hospenthal) and Veterans Hospital, Washington, DC (Virginia Kan); Coopers Hospital, Camden, New Jersey (Annette Reboli); Yale University, New Haven, Connecticut (Brian Wong); Minneapolis Veterans Af-

fairs Medical Center (V.A.M.); and Oregon Health Science Center, Portland (Michael Martin).

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