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
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 at each site according to whether death was due to chronic necrotizing aspergillosis, aspergilloma, or ABPA.

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 clinical 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 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 10 or more 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 1 case of aspergilloma, and 5 of these centers reported 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.

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

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.

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

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

<table>
<thead>
<tr>
<th><em>Aspergillus</em> species</th>
<th>Invasive disease (n = 256)</th>
<th>Chronic necrotizing aspergillosis (n = 41)</th>
<th>Aspergiloma (n = 83)</th>
<th>ABPA (n = 87)</th>
<th>Colonization (n = 735)</th>
<th>Contamination (n = 275)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>A. flavus</em></td>
<td>41 (16)</td>
<td>1 (2)</td>
<td>2 (2)</td>
<td>5 (6)</td>
<td>66 (9)</td>
<td>29 (10)</td>
</tr>
<tr>
<td><em>A. fumigatus</em></td>
<td>171 (67)</td>
<td>33 (80)</td>
<td>57 (69)</td>
<td>80 (92)</td>
<td>465 (63)</td>
<td>102 (37)</td>
</tr>
<tr>
<td><em>A. nidulans</em></td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td><em>A. niger</em></td>
<td>14 (5)</td>
<td>4 (10)</td>
<td>11 (13)</td>
<td>0 (0)</td>
<td>101 (14)</td>
<td>66 (24)</td>
</tr>
<tr>
<td><em>A. terreus</em></td>
<td>8 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>8 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1)</td>
<td>3 (8)</td>
<td>4 (5)</td>
<td>0 (0)</td>
<td>28 (4)</td>
<td>17 (6)</td>
</tr>
<tr>
<td>Not identified</td>
<td>18 (7)</td>
<td>0 (0)</td>
<td>9 (11)</td>
<td>2 (2)</td>
<td>62 (8)</td>
<td>58 (21)</td>
</tr>
</tbody>
</table>

**NOTE.** ABPA, allergic bronchopulmonary aspergillosis.
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 aspergiloma, 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 aspergiloma 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 6. Risk of invasive aspergillosis (IA) among patients whose cultures were positive for *Aspergillus* species.

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

NOTE. A case can be included in >1 disease classification. BMT, bone marrow transplant.

*a* 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 galactomannan [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 >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.

<table>
<thead>
<tr>
<th>Group, characteristic (no. of patients)</th>
<th>Percentage of patients dead at 3 months, according to cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspergillosis</td>
</tr>
<tr>
<td>Disease classification</td>
<td></td>
</tr>
<tr>
<td><em>Aspergillus</em> colonization (508)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>IA (148)</td>
<td>40</td>
</tr>
<tr>
<td>Risk</td>
<td></td>
</tr>
<tr>
<td>Allogeneic BMT (39)</td>
<td>39</td>
</tr>
<tr>
<td>Autologous BMT (14)</td>
<td>29</td>
</tr>
<tr>
<td>Neutropenia (61)</td>
<td>34</td>
</tr>
<tr>
<td>Hematologic cancer (106)</td>
<td>27</td>
</tr>
<tr>
<td>Solid-organ cancer (124)</td>
<td>5</td>
</tr>
<tr>
<td>Corticosteroid use (381)</td>
<td>11</td>
</tr>
<tr>
<td>Treatment for IA</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B (95)</td>
<td>38</td>
</tr>
<tr>
<td>Itraconazole (43)</td>
<td>21</td>
</tr>
</tbody>
</table>

NOTE. BMT, bone marrow transplant; IA, invasive aspergillosis.
and Dummer [48], using risk stratification, found that a pos-
itive 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 cul-
mination of risk factors, such as prolonged neutropenia, cor-
ticosteroid use, prolonged antibacterial administration, cyto-
toxic 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 doc-
umented 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+ 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 pos-
itive 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 immunosup-
pression 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 Asper-
gillus species. However, these cases may be impacted by As-
pergillus 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 ele-
vates the risk of IA [65–67]. Aspergillosis in lung transplants
may assume 3 forms—anastomotic infection, tracheobronchiti-
sis, 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 corti-
costeroid therapy [70].

Successful management of IA remains a great challenge. De-
spite 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, amphi-
tericin 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 am-
photericin 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 col-
onization 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 un-
derlying 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 sup-
ported 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 sug-
gest 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 aspergilomas, 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 Reboi); 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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References

18. Glimp R, Bayer A. Pulmonary aspergillomas: diagnostic and thera-
criteria for the diagnosis of allergic bronchopulmonary aspergillosis.
20. Chandrasekar PH, Alangaden G, Manavathu E. Aspergillosis: an increas-
21. Dasbach EJ, Davies GM, Teutsch SM. Burden of aspergillosis-related
immunodeficiency virus-negative patients in the era of effective azole
Outbreak of systemic aspergillosis in a neonatal intensive care unit.
Loewenich V. Invasive pulmonary aspergillosis in a critically ill neonate:
case report and review of invasive aspergillosis during the first 3 months of
25. Sutton DA, Sanche SE, Revankar SG, Forthglaw AW, Rinaldi MG. In
vitro amphotericin B resistance in clinical isolates of Aspergillus terreus
with head-to-head comparison to voriconazole. J Clin Microbiol
26. Iwen PC, Rupp ME, Langnas AN, Reed EC, Hinrichs SH. Invasive
pulmonary aspergillosis due to Aspergillus terreus: 12-year experience
27. Duthie R, Denning DW. Aspergillus fumigatus fungemia: report of 2 cases and
28. Kontoyiannis DP, Sumoza D, Tarrand JJ, et al. Significance of asper-
in patients without prior cardiac surgery. Medicine (Baltimore) 2000;
79:261–8.
30. Mylonakis E, Paliou M, Sax PE, Skolnik PR, Baron MJ, Rich JD. Central
airways: radiographic, CT and pathologic findings. Radiology
32. Knutsen AP, Slavin RG. Allergic bronchopulmonary mycosis compli-
33. Patterson R, Greenberger PA, Halvig M, et al. Allergic bronchopul-
monary aspergillosis: natural history and classification of early disease
by serologic and roentgenographic studies. Arch Intern Med 1986; 146:
916–8.
34. Washburn RG, Kennedy DW, Begley MG, Henderson DK, Bennett JE.
Chronic fungal sinusitis in apparently normal hosts. Medicine (Balti-
tomore) 1988; 67:231–47.
35. Young RC, Bennett JE, Vogel CL, Carbone PP, DeVita VT. Asper-
gillus: the spectrum of the disease in 98 patients. Medicine (Bal-
37. Pannuti CS, Gingrich RD, Pfaffer MA, Wenzel RP. Nosocomial pneu-
monia in adult patients undergoing bone marrow transplantation: a
38. Shpilberg O, Dover D, Goldschmied-Reouven A. Invasive aspergillosis
in neutropenic patients with hematologic disorders. Leuk Lymphoma
39. Nalesnick MA, Myerogil RL, Jenkins R. Significance of Aspergillus spe-
cies isolated from respiratory secretions in the diagnosis of invasive pulmonary
40. Kahn FW, Jones JM, England DM. The role of bronchoalveolar lavage
in the diagnosis of invasive pulmonary aspergillosis. Am J Clin Pathol
41. Horvath JA, Dummer S. The use of respiratory-tract cultures in the
diagnosis of invasive pulmonary aspergillosis. Am J Med 1996; 100:
171–8.
42. Yu VL, Muder RR, Poorsattar A. Significance of isolation of Aspergillus
from the respiratory tract in diagnosis of invasive pulmonary asper-
of invasive aspergillosis after allogeneic bone marrow transplantation.
44. Iwen PC, Reed EC, Armitage JO, et al. Nosocomial invasive aspergillosis
in lymphoma patients treated with bone marrow or peripheral stem
infections in a large cohort of patients undergoing bone marrow trans-
46. Yuen KY, Woo PCY, Ip MSM, et al. Stage-specific manifestation of
mold infections in bone marrow transplant recipients: risk factor and
clinical significance of positive concentrated smears. Clin Infect Dis
47. Wallace JM, Lim R, Browdy BL, et al. Risk factors and outcomes as-
soiated with identification of Aspergillus in respiratory specimens from
persons with HIV disease. Pulmonary Complications of HIV Infection
U. Changing role of invasive aspergillosis in AIDS: a case control study.
49. Mylonakis E, Barlam TF, Flanagan T, Rich JD. Pulmonary aspergillosis
and invasive disease in AIDS: review of 342 cases. Chest 1998; 114:
251–62.
Medicine 1999; 78:123–32.
51. Singh N, Arnow PM, Bonham A, et al. Invasive aspergillosis in liver
52. Horvath JA, Katzman BA, Stalder J, et al. Incidence and significance of
aspergillosis cultures following liver and kidney transplantation.
54. Shpilberg O, Dover D, Goldschmied-Reouven A. Invasive aspergillosis
in renal transplant patients: correlation with corticosteroid therapy. J Infect Dis