Therapeutic Outcome in Invasive Aspergillosis

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A review of series of ≥4 cases of invasive aspergillosis (total, 1,223 cases) was undertaken to establish the crude mortality and rate of response to therapy with amphotericin B in the major at-risk host groups. In association with pulmonary, sinu-, and cerebral aspergillosis in immunocompromised patients, the crude mortality rates were 86%, 66%, and 99%, respectively. No untreated patient survived. Among 84 patients treated for 1–13 days, only one survived. Among those with invasive pulmonary aspergillosis treated for ≥14 days, the response rates to amphotericin B deoxycholate were 83% (in cases of heart and renal transplantation), 54% (leukemia), 33% (bone marrow transplantation) and 20% (liver transplantation). Patients with AIDS mostly received both amphotericin B and itraconazole, and 37% of those treated for ≥14 days responded to therapy. Substantial variation in outcome from series to series was related to underlying disease status, site of disease, and management. Invasive aspergillosis remains a devastating opportunistic infection despite current treatment.

Invasive aspergillosis is an increasingly frequent disease in immunocompromised patients. From 1970 to 1976 there was a 160% increase in cases of invasive aspergillosis diagnosed at autopsy in the United States [1]. An 8-year autopsy survey of 200,532 cases showed a more than twofold increase in cases of invasive aspergillosis from 1972 to 1980 [2]. More recent data, from 11,000 autopsy cases in Germany, showed an increase in the percentage of all mycoses revealed at autopsy (from 1.5% to 6%) and a proportional increase in cases of invasive aspergillosis (from 17% to 60%) over the years 1978–1992 [3]. Among cancer patients worldwide, invasive aspergillosis was found in 30% at autopsy [4].

There are probably many factors responsible for this substantial increase, but they include the following: greater numbers of transplantation patients; more aggressive chemotherapy for such conditions as myeloma, breast cancer, and certain lymphomas; more aggressive immunosuppressive regimens for patients with autoimmune disease; and the emergence of AIDS.

Only two antifungal agents are effective for the treatment of invasive aspergillosis: amphotericin B and itraconazole. The first report on the use of amphotericin B for this indication was published in 1959 [5], and that of itraconazole was published in 1987 [6]. Studies of newer modes of administration of amphotericin B—in liposomes or associated with cholesteryl sulfate or other lipids—have shown that these compounds also have efficacy in cases of invasive aspergillosis [7–10]. However, no randomized studies of invasive aspergillosis have been successfully concluded.

Six years ago Dr. David Stevens and I attempted to summarize the available data on the treatment of invasive aspergillosis, both medical and surgical, by collating the available data from case reports and series [11]. We excluded from this analysis all patients who had been treated for <14 days, because we felt that the relative efficacy of treatment could not easily be assessed in less time. Other investigators have criticized this approach because a substantial number of early deaths have occurred in cases of invasive aspergillosis (in addition to the deaths of many patients who are not treated), and the response rates we reported might therefore have been overly optimistic.

Given the availability of new compounds for the treatment of invasive aspergillosis, it becomes critically important to define a benchmark against which compounds can be judged and, in particular, a basis for planning randomized controlled trials. This article is an attempt to provide this scientific basis.

Methods

All published series of invasive aspergillosis that included ≥4 patients were reviewed. Case reports of ≤3 cases were excluded because of the likelihood of a bias in favor of successful therapy or because of the novelty of the clinical manifestations or diagnostic approach. Within each series individual cases were selected only if they fulfilled criteria for definite or probable invasive aspergillosis, as previously described [12], with the following modifications.

For immunocompromised patients a blood culture positive for Aspergillus fumigatus, in association with a radiological abnor-
mality in the chest, was accepted as proof of a definitive case of invasive aspergillosis [13]. For bone marrow transplantation and neutropenic patients whose CT scan showed a pulmonary cavitory process or the halo sign, in association with clinical features typical of invasive aspergillosis [14–16], the diagnosis was considered probable. Tracheobronchial disease was included among cases of invasive pulmonary aspergillosis.

Patients were classified by their worst immunocompromising factor, so all leukemic patients who had received a bone marrow transplant were included in the latter group. In most reports it was not possible to determine which transplantation procedure had been done, so all transplantations were included in the bone marrow transplantation group. Patients with lymphoma were included in the bone marrow transplantation group if they had undergone transplantation or in the leukemic group if they were neutropenic. Patients in the lung transplantation group included single and double lung transplant recipients and heart-lung transplant recipients. With respect to the cerebral aspergillosis cases, only a few patients did not appear to be immunocompromised, and these are listed separately.

Cases were excluded if they were treated exclusively by surgery, but not if resection surgery was accompanied by medical therapy; there were fewer than 10 such cases. Cases were also excluded if insufficient outcome data were provided. With respect to the analysis of crude mortality, patients who were treated with amphotericin B deoxycholate with or without flucytosine or rifampin, itraconazole, or liposomal amphotericin B have been included. Some were treated with ≥2 agents sequentially.

Two assessments of outcome were made: crude mortality and response to treatment. Crude mortality was assessed irrespective of whether treatment was or was not given. All patients who died of invasive aspergillosis within 3 months of its diagnosis were included in the number of deaths. If reports did not give data from up to 3 months following diagnosis, patients were classified as survivors only if they were successfully treated.

The response to treatment, as related to its duration, was assessed with regard to amphotericin B deoxycholate only, with one exception: for patients with AIDS the combination of amphotericin B and itraconazole was assessed, as most of these patients received both. No assessment of outcome (other than crude mortality) was made for patients who received any lipid-associated preparation of amphotericin B. When reports stated the total dose of amphotericin B but not the duration of therapy, the dosage was assumed to have been 0.8–1 mg/(kg · d).

Patients treated with a combination of flucytosine or rifampin and amphotericin B were included in the analysis. Empirical amphotericin B therapy (as for febrile neutropenia) was included in calculations of the duration of therapy. Patients who survived for >3 months after the initiation of therapy were classified as responders, even though some subsequently died following partial or complete responses to amphotericin B.

Only three sites of infection, the commonest sites of invasive aspergillosis, were assessed: the lung, brain, and sinuses (including the nose). Infections involving multiple sites were classified according to that which determined the outcome; that is, a case of cerebral and pulmonary disease was specified as cerebral, and that of rhinosinusitis and pulmonary disease was classified as pulmonary.

Results

The crude mortality associated with invasive pulmonary aspergillosis varied with the host group and within each host group (table 1). The mean mortality rate among the reports of bone marrow transplantation patients (including recipients of autologous, allogeneic, and peripheral stem cell transplants) was 90% but varied from 33% to 100%. If data from the series in which treatment details were not given are excluded, this figure falls to 87% (with the same range). This group of patients included those who were neutropenic shortly after transplantation and those in whom invasive pulmonary aspergillosis developed after the neutrophil count recovered but in the context of graft-versus-host disease. Most of the patients died rapidly, before or just after diagnosis.

In the context of leukemia and neutropenia following cytotoxic chemotherapy and aplastic anemia, the mean mortality was 77% (range, 13%–100%), rather lower than that after bone marrow transplantation. Among the 279 patients who were treated in this context, the mean crude mortality was 67%, a figure suggesting that treatment has a measurable benefit.

Most of the cases of invasive aspergillosis in renal transplantation patients occurred in the preyclosporin era; this disease is now relatively infrequent among renal transplant recipients. A 100% success rate was recorded for four patients treated with itraconazole, but the experience with this small series contrasts with early data indicating a mortality range of 78%–100%. Renal transplantation is probably the only transplantation setting in which immunosuppression can be stopped and a graft sacrificed because of the availability of renal replacement therapy. In one series of 10 survivors of invasive aspergillosis, the grafts of four failed and were removed surgically [56]. Clearly, a substantial reduction in immunosuppression may have a profound, positive influence on outcome.

Heart transplant recipients were distinguished primarily by substantially lower mortality as compared with other host groups, namely, 50% (range, 11%–78%). Amongst the 36 patients who were treated, the mortality was 44%.

In patients who have received either lung or heart-lung transplant, distinguishing colonization from disease can be difficult. In addition, there is perhaps a higher incidence of airway disease [64] in these patients than in other host groups, and this may have a different outcome from that of pulmonary parenchymal disease. Few patients with invasive aspergillosis following lung transplantation are described in the literature, and it is difficult to draw any conclusions from this slight experience.
Table 1. Crude mortality associated with invasive aspergillosis, according to patient group and site of disease.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>No. of cases reported</th>
<th>Treated (any agent, any duration)</th>
<th>Who died with or of aspergillosis</th>
<th>Crude mortality rate per series (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary aspergillosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow transplantation</td>
<td>254</td>
<td>167*</td>
<td>229</td>
<td>33–100 (90)</td>
<td>[7, 12, 17–30]</td>
</tr>
<tr>
<td>Leukemia, neutropenia, and aplastic anaemia</td>
<td>407</td>
<td>279*</td>
<td>315</td>
<td>13–100 (77)</td>
<td>[7, 12, 31–53]</td>
</tr>
<tr>
<td>Renal transplantation</td>
<td>63</td>
<td>20*</td>
<td>44</td>
<td>0–100 (70)</td>
<td>[47, 54–58]</td>
</tr>
<tr>
<td>Heart transplantation</td>
<td>64</td>
<td>36*</td>
<td>32</td>
<td>11–78 (50)</td>
<td>[59–63]</td>
</tr>
<tr>
<td>Lung transplantation</td>
<td>13</td>
<td>6*</td>
<td>10</td>
<td>50–100 (77)</td>
<td>[64, 65]</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>61</td>
<td>31*</td>
<td>57</td>
<td>57–100 (93)</td>
<td>[58, 66–71]</td>
</tr>
<tr>
<td>AIDS</td>
<td>115</td>
<td>78</td>
<td>93</td>
<td>36–100 (81)</td>
<td>[12, 72–81]</td>
</tr>
<tr>
<td>Aspergillus rhinosinusitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia, neutropenia, and bone marrow transplantation</td>
<td>90</td>
<td>90</td>
<td>59</td>
<td>17–85 (66)</td>
<td>[28, 29, 82–89]</td>
</tr>
<tr>
<td>Cerebral aspergillosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>141</td>
<td>64*</td>
<td>140</td>
<td>86–100 (99)</td>
<td>[12, 17, 28, 29, 35, 56, 62, 90–98]</td>
</tr>
<tr>
<td>Nonimmunocompromised</td>
<td>15</td>
<td>15</td>
<td>2</td>
<td>0–17 (13)</td>
<td>[12, 95, 96]</td>
</tr>
</tbody>
</table>

* Numbers represent the minimum number treated; other patients were probably treated, but this is not stated in the reports.

Invasive aspergillosis following liver transplantation is associated with high mortality. The crude mortality in this analysis varied between 57% and 100% (overall mean, 93%). The best outcomes were reported by Rossi et al., and one notable factor was their initiation of treatment when cytological or cultural evidence of invasive aspergillosis was first revealed [70], which was not true of the other series. It may be that this was a factor giving rise to a better outcome. In addition, this is the only series in which itraconazole was used. Amongst those patients who were treated, the mortality was 87%.

An increasing number of patients with AIDS and invasive aspergillosis are being reported. In many respects, this group of patients differs from the other major risk groups in that their underlying disease is progressive and incurable. Crude mortality, therefore, will prove to be 100% if follow-up is extended for a long enough period. In this review I chose 3 months as the time of estimation of crude mortality, although this period was extended for cases in which it was clear that invasive aspergillosis was the primary reason for death. Despite these limitations, the crude mortality was high—usually close to 100%, with a mean of 81%—among 115 patients. Among treated patients with AIDS, the crude mortality was 72%.

Invasive aspergillus rhinosinusitis occurs primarily in leukemic and bone marrow transplant patients. In nine series in the literature, all 90 patients had the benefit of treatment, a circumstance demonstrating the greater case with which a diagnosis can be made in cases involving this accessible part of the body. Despite this fact, the crude mortality was 66% (range, 17%–85%). As all patients received treatment, it was clear that there was only a 34% response to treatment. The best results appeared to be obtained in a small series of patients whose conventional therapy with amphotericin B failed and who were subsequently treated with a multilamellar form of liposomal amphotericin B [86]. However, this experience was with only six patients, and no further data on this amphotericin B preparation are available.

With respect to cerebral aspergillosis, there is a clear difference in outcome between immunocompromised and nonimmunocompromised patients, as shown in table 1. Among the 141 immunocompromised patients with cerebral aspergillosis, 140 died, a mortality rate of 99%. In contrast, only two of the 15 nonimmunocompromised patients died, a mortality rate of 13%.

Responses to therapy as related to its duration for invasive aspergillosis in various host groups are shown in table 2. All untreated patients died, and, likewise, all those treated for <8 days died. One (8%) of 13 leukemic patients treated for <14 days responded, but among those who lived long enough to receive 14 days of therapy, 54% responded. Better response rates were recorded for renal and heart transplant recipients, and worse responses for liver and bone marrow transplant recipients and patients with AIDS.

A similar picture is seen with aspergillus rhinosinusitis, in which 14 days’ therapy appeared to be the minimum required for a response rate of ~50%. At least 11 of the responders were cured of their infection; in contrast, all nonresponders died immediately or subsequently of complications of leukemia, bone marrow transplantation, or invasive aspergillosis.

With respect to cerebral aspergillosis, it is clear that for the majority of patients the diagnosis is not established before death.
Table 2. Response to therapy with amphotericin B deoxycholate, as related to its duration, among patients with invasive aspergillosis.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Untreated</th>
<th>1 - 7 d</th>
<th>7 - 13 d</th>
<th>≥14 d</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary aspergillosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow transplantation</td>
<td>0/3</td>
<td>0/5</td>
<td>0/4</td>
<td>5/15 (33)</td>
<td>[17, 20, 25, 26]</td>
</tr>
<tr>
<td>Leukemia, neutropenia, and aplastic anemia</td>
<td>0/36</td>
<td>0/20</td>
<td>1/13 (8)</td>
<td>44/81 (54)</td>
<td>[20, 31 - 36, 41 - 44, 48, 49]</td>
</tr>
<tr>
<td>Renal transplantation</td>
<td>0/17</td>
<td>0/0</td>
<td>0/0</td>
<td>10/12* (83)</td>
<td>[54 - 56]</td>
</tr>
<tr>
<td>Heart transplantation†</td>
<td>0/1</td>
<td>0/0</td>
<td>0/0</td>
<td>10/12 (83)</td>
<td>[59, 63]</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>0/4</td>
<td>0/1</td>
<td>0/1</td>
<td>1/5 (20)</td>
<td>[68 - 71]</td>
</tr>
<tr>
<td>AIDS</td>
<td>0/40</td>
<td>0/14</td>
<td>0/7</td>
<td>20/54 (37)</td>
<td>[12, 72 - 81]</td>
</tr>
<tr>
<td>Invasive aspergillus rhinosinusitis</td>
<td>0/0</td>
<td>0/8</td>
<td>0/3</td>
<td>17/35 (49)</td>
<td>[26, 82, 85 - 89]</td>
</tr>
<tr>
<td>Cerebral aspergillosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immuno compromised</td>
<td>0/49</td>
<td>0/4</td>
<td>0/4</td>
<td>0/7</td>
<td>[17, 35, 56, 90 - 94, 96, 97]</td>
</tr>
<tr>
<td>Nonimmuno compromised</td>
<td>0/1</td>
<td>0/0</td>
<td>0/0</td>
<td>3/9 (33)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Only amphotericin B deoxycholate was given, except to patients with AIDS, most of whom received both amphotericin B and itraconazole.
* In 4 of 10 survivors, the renal allograft failed because of a reduction in immunosuppression and amphotericin B therapy.
† All 7 patients in one series [60] died despite therapy with amphotericin B deoxycholate, but the amount given was not stated.

Discussion

The data given above are a depressing litany of poor outcomes of invasive aspergillosis. Several factors, aside from organ involvement and host group, have been described that are probably important in determining the outcome of invasive aspergillosis. These are listed in table 3.

In leukemic patients, recovery from neutropenia and remission of leukemia are key factors. In transplantation patients, reduction of immunosuppressive therapy (if possible) may be important. The pattern of invasive pulmonary aspergillosis is also important. Focal peripheral disease that does not cavitate is predictive of a more favorable response, whereas diffuse disease or centrally placed focal disease is associated with a poor outcome. Cavitation is associated with hemoptysis that is often fatal, although it may not be if emergency thoracotomy and lobectomy can be undertaken [104].

The time of initiation of appropriate antifungal therapy is probably critical for all patients, but it is particularly so for those whose immunodeficiency (e.g., neutropenia) will not be diminished. The dosage of amphotericin B deoxycholate given to neutropenic patients is important and should be at least 1 mg/(kg · d). With respect to itraconazole, an adequate dosage (e.g., ≥400 mg/d) and absorption are vital for a response. As failure rates are high, switching the antifungal therapy early when the first treatment choice fails may be important.

The outlook in cases of chronic invasive aspergillosis is also poor, partly because of the frequent coexistence of severe pulmonary disease. Insufficient data have been published to generate useful analyses of response [47, 106 - 109]. It is not yet clear whether itraconazole or one of the lipid-associated amphotericin B preparations (e.g., AmBisome [Nexstar, San Dimas, CA], Amphocil [ABCD; Sequus Pharmaceuticals, Menlo Park, CA], or Abelcet [ABLC; The Liposome Company, Princeton, NJ]) is superior to conventional amphotericin B for treatment of invasive aspergillosis. It is clear that patients for whom therapy with amphotericin B fails do sometimes respond to itraconazole or a lipid-associated amphotericin B preparation. In addition, there are some suggestions from the above data that Amphocil, AmBisome, and itraconazole may be superior to amphotericin B deoxycholate in the sense that the crude mortality figures associated with the use of these agents are considerably lower than those associated with use of amphotericin B.
For example, for none of four renal transplant recipients with invasive aspergillosis did therapy with itraconazole fail, whereas a 50%–100% failure rate occurred with use of amphotericin B deoxycholate. Six of seven patients with persistent neutropenia (for >7 days; median, 21 days) responded to itraconazole [12], whereas virtually no responses to amphotericin B deoxycholate among such patients have been recorded in the literature. Likewise, at least three persistently neutropenic patients are reported to have had a complete response to AmBisome [7].

Better responses to itraconazole than to amphotericin B were seen in one small randomized study, but the difference was not statistically significant, and the doses of both agents were low [109]. This observation may of course reflect other factors, such as a pattern of invasive aspergillosis that is easier to diagnose (e.g., focal disease) and the known propensity for patients in clinical trials to do better overall than the general population of such patients. It could also reflect other improvements in management related to investigative sites or patient populations at these sites.

This last point is also suggested by the remarkably low mortality (13%) associated with invasive pulmonary aspergillosis in one series, in which large doses (1.25–1.5 mg/[kg · d]) of amphotericin B deoxycholate were given with flucytosine [44]. Nonetheless, the prevailing data suggest that substantial improvements in response rates and mortality can occur with alternative therapy when amphotericin B deoxycholate fails or cannot be tolerated, and the availability of new agents for this frequently fatal opportunistic mycosis are welcome.

Of course, the next step following the first multicenter trial of therapy for invasive aspergillosis is the randomized comparative trial. Two small trials have been reported [52, 110], both with insufficient power, and at least four such trials have been launched. One ongoing trial being undertaken by the European Organization for Research and Treatment of Cancer (Invasive Fungal Infections Cooperative Group) is comparing two doses of AmBisome administered to neutropenic patients with probable or confirmed invasive aspergillosis. Recruitment was completed in autumn 1995. Another double-blind randomized study comparing Amphocil with amphotericin B deoxycholate is ongoing in the United States and Europe.

However, there are substantial difficulties in organizing a randomized trial of treatment for invasive aspergillosis. The number of bona fide cases, while increasing substantially, is relatively small, and cases are scattered amongst multiple institutions. The multiple lipid-associated amphotericin B preparations now available (in Europe) create a problem with regard to what constitutes standard therapy. For example, Amphocil and AmBisome are now routinely used as first-line therapy for transplant recipients to avoid synergistic renal toxicity with use of cyclosporin. Response rates associated with different host groups and sites of disease indicate a need for some stratification, possibly increasing the study size. There are also major differences in practice with respect to the speed and mode of diagnosis in different institutions.

Several questions related to host factors that are major determinants of outcome are unanswerable at randomization, e.g., how long neutropenia will last and whether leukemia will go into remission. These disease-related factors are further exacerbated by the introduction and wide use of colony-stimulating factors, which can shorten the duration of neutropenia and improve the function of neutrophils and macrophages in vitro.

Many responses to therapy are incomplete, and both therapy and observation have to be continued for months and sometimes years for a good clinical result. Determination of a meaningful mycologic endpoint is problematic, and at present only clinical and radiological endpoints are useful [12].

Despite these difficulties, it is absolutely necessary to do randomized studies of treatment for invasive aspergillosis. Given the changing face of immunosuppression in many contexts, the increasing number of cases, and the high mortality associated with invasive aspergillosis, large cooperative trials are justified and necessary.

References