MAJOR ARTICLE

Aspergillosis Case-Fatality Rate: Systematic Review of the Literature

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To update the case-fatality rate (CFR) associated with invasive aspergillosis according to underlying conditions, site of infection, and antifungal therapy, data were systematically reviewed and pooled from clinical trials, cohort or case-control studies, and case series of ⩾10 patients with definite or probable aspergillosis. Subjects were 1941 patients described in studies published after 1995 that provided sufficient outcome data; cases included were identified by MEDLINE and EMBASE searches. The main outcome measure was the CFR. Fifty of 222 studies met the inclusion criteria. The overall CFR was 58%, and the CFR was highest for bone marrow transplant recipients (86.7%) and for patients with central nervous system or disseminated aspergillosis (88.1%). Amphotericin B deoxycholate and lipid formulations of amphotericin B failed to prevent death in one-half to two-thirds of patients. Mortality is high despite improvements in diagnosis and despite the advent of newer formulations of amphotericin B. Underlying patient conditions and the site of infection remain important prognostic factors.

The first case of invasive aspergillosis reported in an immunocompromised patient occurred in 1953, concurrent with the introduction of corticosteroids and cytotoxic chemotherapy into the medical armamentarium [1]. Invasive aspergillosis continues to pose a significant threat to immunocompromised patients. In the United States, a 160% increase in cases of aspergillosis has been reported in an autopsy series from 1960 through 1970 [2]. Similarly, in Germany, a review of 11,000 autopsy cases from 1978 through 1992 demonstrated a 17%–60% proportional increase in cases of invasive aspergillosis [3].

The profile of patients considered at risk for invasive aspergillosis continues to expand, a finding that is explained by the use of aggressive and intensive chemotherapeutic regimens for solid tumors and other hematologic malignancies, increases in the number of bone marrow and solid-organ transplantations performed, use of immunosuppressive regimens for treatment of autoimmune diseases, and the HIV/AIDS pandemic [4]. Denning [5] recently reviewed the therapeutic outcome in 1223 cases of invasive aspergillosis from 1972 through 1995. Case-fatality rates (CFRs) were 99%, 86%, and 66% for cerebral, pulmonary, and sinus aspergillosis, respectively. In Denning's review, therapeutic outcome varied according to underlying disease, site of infection, and antifungal management.

Despite perceived advances in current treatment, invasive aspergillosis remains a devastating opportunistic infection. We conducted a systematic review of the literature to establish the CFR for invasive aspergillosis in studies reported after 1995, to determine whether any prognostic factors, including advances in antifungal therapy, may have affected these staggering mortality statistics.

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METHODS

Source of data. Data from the available medical literature were systematically reviewed and pooled to evaluate the CFR of *Aspergillus* infection. Relevant studies published in the English-language literature in or after 1995 were retrieved by use of "aspergillosis" as either a keyword or MeSH (medical subject heading) term in searches of the MEDLINE (US National Library of Medicine, Bethesda, MD) and EMBASE (Elsevier Science, New York, NY) bibliographic databases. The studies analyzed were randomized controlled clinical trials, case-control studies, cohort studies, or case series performed in North America, Europe, and Japan. To reduce reporting bias, only studies that involved $\geq$10 cases of *Aspergillus* infection and that reported outcomes as fatal or nonfatal were included. Patient demographics and potential prognostic factors, including underlying disease, infection site, neutrophil count, and treatment provided, were recorded for further analysis.

Definitions. We included cases of definite and probable aspergillosis on the basis of the clinical assessment of the authors, which proved consistent with the following case definitions. A case was regarded as "definite" when the histopathologic evidence for invasive aspergillosis in a tissue specimen was established and *Aspergillus* species was documented in culture. A case was regarded as "probable" (1) if there was histopathologic evidence for invasive aspergillosis but cultures either failed to yield the organism or were not obtained, or (2) in the absence of histopathology, a positive culture result was obtained for a specimen from a normally sterile site (e.g., the lung) resulting from a clinically or radiologically suspicious lesion. On the basis of the site of infection, we categorized aspergillosis as follows: invasive pulmonary aspergillosis, which was reported as primarily diffuse involvement or primarily localized disease, such as a focal lesion reported as an air crescent or halo sign or aspergilloma; other respiratory tract sites, such as sinus or airway; CNS; disseminated; multisite; or other site (e.g., of the skin and eyes). Aspergillosis was defined as disseminated if an infection involved >1 noncontiguous site reflecting blood-borne spread, whereas the infection was classified as multisite if the sites of infection that were involved were within 1 organ system, such as the lung and sinus or the trachea and sinus within the respiratory tract.

Underlying diseases and comorbidities extracted from the studies included hematologic malignancies (e.g., leukemia and lymphoma), solid-organ malignancies, bone marrow and solid-organ transplants, HIV infection or AIDS, systemic steroid use and other immunosuppressive treatments, and pulmonary disease, such as previous tuberculosis or chronic obstructive pulmonary disease. Neutropenic status, which was defined as an absolute neutrophil count of <500 cells/mm^3, was also coded when the data were available.

Intravenous amphotericin B, lipid formulations of amphotericin B deoxycholate (e.g., liposomal amphotericin [AmBisome; Fujisawa] or amphotericin B colloidal dispersion [Abelcet; Liposome]), and oral itraconazole were coded as antifungal treatments for aspergillosis. Other antifungals, such as flucytosine, fluconazole, and investigational agents, were also coded if the information was noted in the study. All therapy was included, regardless of duration. Patients were classified as receiving local therapy if they were treated with surgical procedures or other local therapies, such as percutaneous or intracavitary instillation of an antifungal agent, with or without the concomitant use of other systemic antifungal therapy.

Data extraction and quality control. A medical information scientist performed the literature retrieval and the initial screening of relevant studies, and a pharmacist reviewed and coded all studies. Studies were scrutinized to exclude any duplicate reports of the same patients. Two physicians, one who specialized in infectious disease and the other in epidemiology, checked data from a random sample of studies for reliability. Discrepancies were resolved, and review was iterated until interrater reliability was high.

Many studies reported only aggregate results. Whenever possible, data were extracted both at an aggregate level within each study and at a patient level. Data extracted at the patient level provided more-detailed information about underlying diseases, treatment, site of infection, and outcomes.

The end points of the study were patient deaths and the crude CFR associated with invasive aspergillosis. Potential prognostic determinants that were coded included patient demographics, underlying disease and condition, degree and duration of neutropenia, site of the *Aspergillus* infection, and treatments administered for both the underlying disease(s) and *Aspergillus* infection itself.

Analysis. The data were pooled at both the aggregate and patient levels to determine the distribution of underlying disease, site of infection, treatments, and other pertinent variables. CFRs were estimated on the basis of the pooled data. Variables frequently were not available for all patients. We excluded studies or individuals with missing values from specific analyses. As a result, the number of patients in each analysis varies. Because of the heterogeneity in the study design, statistical analysis of the pooled data from the 50 studies was not undertaken.

RESULTS

A total of 222 studies published from 1995 through 1999 were extracted from the MEDLINE and EMBASE databases on the basis of our inclusion criteria. Of these studies, 169 were excluded from the analysis for the following reasons: 71 had

Table 1. Case-fatality rates, according to age, for patients with aspergillosis (as determined from patient-level data).

Age, y	No. of patients	No. of deaths	CFR, %
⩽20	22	15	68.2
21–30	27	16	59.3
31–40	52	31	59.6
41–50	57	30	52.6
51–60	49	29	59.2
>60	31	17	54.8
Unreported	135	76	56.3

<10 cases, 40 did not have sufficient information on clinical intervention or outcomes (e.g., articles that reported on diagnostic assays), 45 did not report original data (e.g., reviews or comments on previously reported cases), and 13 were not performed in North America, Europe, or Japan. As a result, 53 studies remained in the analysis. A group of patients was reported in 2 articles and another group in 3 articles; we excluded duplicate reports. Therefore, 50 studies (total number of patients, 1941) remained, including 2 controlled clinical trials [6, 7], 3 open-label and noncontrolled clinical trials [8–10], and 45 case-control, cohort, or case series [11–55]. Several studies had been performed among special populations, such as bone marrow transplant recipients [28, 33, 37, 48, 52], solid-organ transplant recipients [16, 21, 25, 41, 42, 51, 54], and patients with HIV infection [11, 43, 46, 49] or hematologic malignancies [8, 12, 34]. The majority of the studies (27 of 50) reported their outcomes in an aggregate manner—that is, without stratification according to underlying disease, comorbidity, or type of infection. Wherever possible, patient-level data were extracted from the other 23 studies, which provided data on 373 patients and thus allowed for more-detailed analyses [10, 11, 13, 15, 26, 27, 29, 31, 32, 34, 36–40, 43, 45, 49–51, 53–55]. Although most studies indicated the criteria for diagnosis, only 4 defined the cases with criteria commonly used in clinical trials that evaluate therapy for invasive aspergillosis; 2 publications used criteria established by the Mycoses Study Group, and the remaining 2 used criteria from the European Organization for the Research and Treatment of Cancer.

All variables were not available for every patient. For example, of the 1941 patients, 990 (51.0%) were male and 575 (29.6%) were female, and the sexes of the remaining 376 patients (19.4%) were not reported. Of the 50 studies, only 26 provided sufficient information on the antifungal regimen given to patients. A total of 22 studies indicated the follow-up period, which ranged from a few days to >103 months in 1 study [12]. In a few studies, missing data resulted from loss of patients to follow-up; however, more often, heterogeneity of detailed clinical event and outcome reporting resulted in incomplete information. Missing values were not imputed, and the analyses were based on available and complete data only. The overall CFR was 58% (1118 of 1941 patients).

Demographics. Sex was reported for 225 of the 373 patients with individual data; 63 (28%) were female and 162 (72%) were male. The CFR for male patients was slightly higher than that for female patients (56.8% vs. 47.6%). Patient age ranged from 3 to 91 years, with a mean of 44.2 years (median, 43 years) and an SD of 30.5 ($n = 238$). There was little variation in mortality by age (table 1).

Underlying conditions. The most commonly reported underlying disease (table 2) was malignancy (44.2%; 858 of 1941), of which lymphoma and leukemia constituted the large majority (827 [42.6%]). Transplants (752 [38.7%]) and lung diseases (388 [20%]), which included pneumonia due to cytomegalovirus, bacterial pneumonia, and tuberculosis, were also common underlying conditions. The aspergillosis CFR varied significantly according to underlying disease or comorbidity. For example, the CFR for patients with leukemia and lym-

Table 2. Underlying conditions among patients with aspergillosis (as determined on the basis of data from 50 studies).

Condition or disease	No. (%) of patients[a] ($n = 1941$)
Bone marrow transplant	500 (25.8)
Solid-organ transplant	
Lung or lung and heart	97 (5.0)
Liver	74 (3.8)
Kidney	21 (1.1)
Other or unspecified	60 (3.1)
Total	252 (13.0)
Cancer	
Solid-organ malignancy	31 (1.6)
Leukemia or lymphoma	827 (42.6)
Total	858 (44.2)
Aplastic anemia	15 (0.8)
HIV/AIDS	73 (3.8)
Immunocompromising disease or condition	
Autoimmune disease	2 (0.1)
Systemic steroid use	65 (3.3)
Total	67 (3.5)
Lung disease or condition	
Cytomegalovirus pneumonia	153 (7.9)
Tuberculosis	82 (4.2)
Chronic obstructive pulmonary disease	26 (1.3)
Other (e.g., emphysema, cystic fibrosis, or bacterial pneumonia)	127 (6.5)
Total	388 (20.0)

[a] A patient could have >1 condition or disease.

phoma (49.3% [142 of 288]) is lower than that for patients with other underlying causes. Conversely, patients with bone marrow transplants had a CFR of 86.7% (247 of 285), a rate higher than that for any other group. Invasive aspergillosis among HIV-infected patients or those with AIDS was also associated with a high CFR, (85.7% [42 of 49]; figure 1).

Site of infection. Seventy percent of the infections were pulmonary. Nearly 9% of patients (175 of 1941) had disseminated and/or CNS aspergillosis. The overall CFR for aspergillosis of all infection sites was 58% (1118 of 1941 patients). This rate is lower than expected because we did not exclude patients who developed chronic necrotizing pulmonary aspergillosis in a preexisting lung cavity (e.g., those with tuberculosis and chronic obstructive pulmonary disease), which represents a distinctly different patient population and prognosis. The patient-level data provided more detail on the CFR by site. The highest CFR rate (88.1% [74 of 84 patients]) occurred among patients with disseminated infection or CNS involvement. The patient-level data indicate that, of the 84 patients with CNS or disseminated aspergillosis, only 10 were reported to be alive at the end of follow-up. Although 51 received amphotericin B, only 7 (12%) survived, compared with 2 (40%) of 5 patients who received lipid formulations of amphotericin B. None of the patients who received either no antifungal therapy (1 patient) or unspecified antifungal therapy (19 patients) survived; no patient was treated with itraconazole. None of the 19 patients (with CNS or disseminated infection) with hematologic malignancies without a bone marrow transplant survived, compared with 7 (14%) of 50 patients with bone marrow transplants. For the remaining 3 survivors, splenectomy, underlying steroid use, or asthma were the underlying illnesses or conditions. In general, these results emphasize that disseminated and CNS aspergillosis exhibited worse prognoses than did localized forms of the disease. Although it was lower than the CFR for disseminated disease, the CFR for pulmonary aspergillosis was >60%. However, patients with localized disease, coded as "aspergilloma," or those with sinusitis, tracheobronchitis, or cutaneous infection had markedly better survival rates (table 3).

The infection site varied according to the underlying condition or comorbidity of the patients (table 4). On the basis of patient-level data, it was determined that recipients of bone marrow transplants were most likely to develop disseminated disease. Patients with hematologic malignancies were more likely to have pulmonary infection, although disseminated aspergillosis also accounted for a significant proportion of disease. However, 47 of the 49 patients with AIDS had *Aspergillus* infections that involved the respiratory tract.

Treatment. Antifungal therapy had limited effectiveness. Patient-level data indicate that more than one-half of the patients died either with or as a result of aspergillosis, despite having received treatment with parenteral amphotericin B, which, at present, is considered the reference standard of therapy. Patients with localized infections (e.g., aspergilloma) were often treated by use of surgical procedures, such as lung resection, or percutaneous administration of amphotericin B. Patients with localized pulmonary disease had a CFR of 24.1%, which is considerably lower than that observed for disseminated disease (table 5). Because antifungal efficacy depends in part on the underlying immune status of the patient, we stratified treatment according to the patient's underlying condition and determined the CFR for each group (table 6).

Neutropenia. Patients with neutrophil counts of <500 cells/mm^3 had lower CFRs (50.7% [154 of 304 patients]) than did those with higher neutrophil counts (72.1% [88 of 122]). Although the number of patients was small, there were no

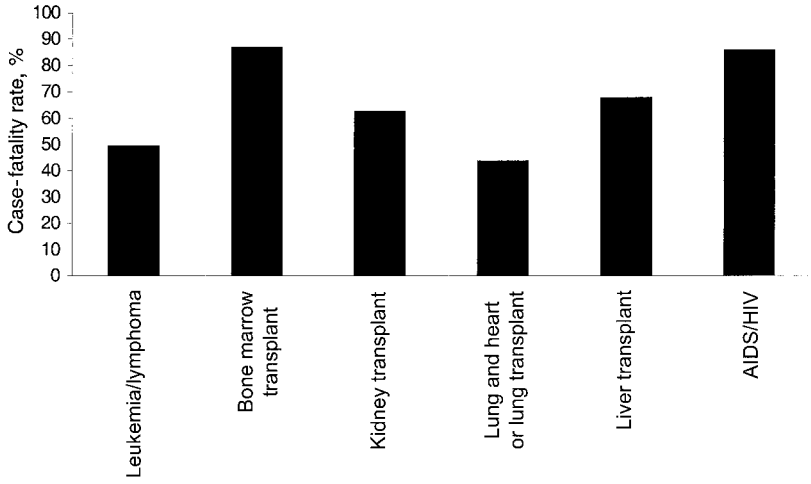

Figure 1. Case-fatality rates for patients with aspergillosis, according to underlying diseases or conditions (as determined from patient-level data)

Table 3. Distribution of patients according to case-fatality rate (CFR) and site of aspergillosis.

Type or site of aspergillosis	No. of cases from study-level data	% Total patients	CFR from patient-level data[a]
Invasive pulmonary			
Diffuse disease	1153	59.4	60.2 (97/161)
Localized disease, including aspergilloma	203	10.5	29.5 (18/61)
Sinusitis	52	2.7	26.1 (6/23)
Tracheobronchitis or other airway	44	2.3	37.5 (3/8)
Multisite	115	5.9	66.7 (10/15)
Disseminated or CNS	175	9.0	88.1 (74/84)
Cutaneous, other, or unspecified	199	10.3	25.0 (4/16)
Total	1941	100.0	57.6 (212/368)[b]

[a] Data in parentheses denote no. of patient deaths/no. of patients with individual data. CFR was based on a total of 368 patients with individual data.

[b] Overall CFR, as determined on the basis of study-level data, was also 57.6% (1118 of 1941 patients).

differences in CFR among patient groups stratified according to the degree and duration of neutropenia.

DISCUSSION

The overall CFR of 58% demonstrates that invasive aspergillosis remains a highly lethal opportunistic infection. Given the severe underlying conditions that predispose patients to aspergillosis, it is difficult to separate deaths due to aspergillosis from those associated with the underlying disease. It is also important to acknowledge the limitations and biases inherent in the study design of this systematic review. These include the use of retrospective data, variable follow-up periods among patients and studies, variable definitions of neutropenia, missing data, the need to use either patient-level or aggregate data for different analyses, inclusion of patients receiving first- and second-line therapy, the small number of cases in some cells, and the lack of a consistent case definition for invasive aspergillosis. As a result of these biases inherent in combining observational studies, statistical analyses were not done.

Our systematic review of the literature identified 1941 patients from recently published studies reporting ⩾10 patients with invasive aspergillosis. We included all studies that required separate aggregate and patient-specific analyses. In contrast, Denning [5] reviewed 1223 cases from series reporting ⩾4 cases of invasive aspergillosis and included only patient-specific data, thus excluding all studies reporting aggregate data. Despite these differences in study design, we observed similar estimates of case fatality and the impact of selected prognostic variables.

The higher prevalence of invasive aspergillosis among males is consistent with male predominance among underlying causes [56]. For example, in 1990–1991, the incidence of leukemia in males and females was 12.3 vs. 7.3 individuals per 100,000 population, respectively. For non-Hodgkin's lymphoma, similar patterns of incidence in males vs. females (83.6 vs. 57.4 individuals per 100,000 population, respectively) were noted. Among renal transplant recipients in 1996, transplants from both cadaveric and living related donors were given to 4714 female patients versus 7014 male patients [57]. The CFR for invasive aspergillosis was modestly higher among male patients than among female patients.

Well-established risk factors for the development of invasive aspergillosis include prolonged neutropenia, underlying lung disease, corticosteroid therapy, immunosuppressive therapy, allogeneic bone marrow transplants [28], and graft-versus-host disease and its treatment [28, 30]. Wherever the data were available and complete, we attempted to evaluate the impact of these selected risk factors within our cohort.

Our review demonstrates that the most common underlying disease associated with invasive aspergillosis was malignancy, with the majority of patients having either leukemia or lymphoma diagnosed. Transplants and chronic lung disease were also significant predisposing conditions, illustrating both the importance of immunosuppression and identification of the lung as a common portal of entry.

Bone marrow transplant recipients had the highest CFR (86.7%), a finding that corroborates Denning's finding of 90% [5]. Of particular concern is the increasing incidence of invasive aspergillosis among bone marrow transplant recipients [48]. In contrast, patients with leukemia or lymphoma had a lower —but still high—CFR of 49.3% (142 of 288). Lower CFRs within the cohort with leukemia or lymphoma may reflect re-

Table 4. Distribution of patients, according to underlying condition and site of aspergillosis (as determined from patient-level data).

Type or site of aspergillosis	No. (%) of patients with an underlying condition			
	Bone marrow transplant	Hematologic malignancy	AIDS or HIV infection	Total
Invasive pulmonary				
Diffuse disease	23 (25.6)	104 (53.3)	30 (61.2)	157 (47.0)
Localized disease, including aspergilloma	3 (3.3)	20 (10.3)	10 (20.4)	33 (9.9)
Sinusitis	5 (5.6)	9 (4.6)	2 (4.1)	16 (4.8)
Tracheobronchitis or other airway	0	0	1 (2.0.)	1 (0.3)
Multisite	9 (10.0)	3 (1.5)	4 (8.2)	16 (4.8)
Disseminated or CNS	48 (53.3)	56 (28.7)	2 (4.1)	106 (31.7)
Cutaneous or other	2 (2.2)	3 (1.5)	0	5 (1.5)
Total	90 (100.0)	195 (100.0)	49 (100.0)	334 (100.0)

covery of cell-mediated immunity after chemotherapy and clinical remission. This CFR for patients with leukemia and lymphoma is lower than the crude mortality of 77% in untreated patients or that of 67% in treated patients described by Denning [5]. Although the reviews should not be directly compared, the lower CFR in our study may be due to inclusion of more-recent studies, possibly reflecting improvements in antifungal therapy or neutropenia management.

Among the solid-organ transplant recipients, the highest CFRs were seen among liver (67.6%) and kidney transplant recipients (62.5%). There was a somewhat lower CFR for lung or lung and heart transplant recipients. Despite the lower CFR, infectious complications accounted for 31% of deaths that occurred within 60 days after lung transplantation. Many centers report an incidence of invasive aspergillosis of up to 16% in lung transplant recipients [25, 54].

The CFR of 85.7% for patients with HIV infection was similar to Denning's finding. There was insufficient information to determine the effect of highly active antiretroviral therapy on immune reconstitution and, therefore, on the CFR. HIV infection portends a poor prognosis because the underlying immunosuppressive condition is progressive and, in most cases, irreversible.

The lung was the most common site of invasive aspergillosis, reflecting the usual portal of entry. Patients with invasive pulmonary aspergillosis that was reported as localized disease had a better prognosis than did those with diffuse disease (CFR, 29.5% vs. 60.2%, respectively). The difference in CFR may reflect an improved host response to *Aspergillus* species (i.e., by formation of a sequestered abscess [5]).

Identification of profiles of patients at risk for developing specific sites of *Aspergillus* infection is clinically useful. In this study, bone marrow transplant recipients were more likely to develop disseminated disease. However, if given a diagnosis of pulmonary disease, bone marrow transplant recipients are more likely to present with diffuse disease rather than localized disease. Invasive aspergillosis in patients with hematologic malignancies most commonly presents as diffuse pulmonary disease, which is followed in frequency by disseminated or CNS disease.

Similar to other immunocompromised cohorts, patients with HIV infection or AIDS are more likely to have invasive pulmonary aspergillosis reported as diffuse, rather than localized, disease (e.g., aspergilloma). Multisite involvement is common in bone marrow transplant recipients and in those with HIV infection or AIDS. In the HIV or AIDS cohort, one would anticipate a decrease in invasive aspergillosis that would be attributable to the effectiveness of highly active antiretroviral therapy. However, the use of cytotoxic chemotherapy for treatment of malignancy or cytomegalovirus disease and the use of corticosteroids for *Pneumocystis carinii* pneumonia and *Mycobacterium avium* complex infection may predispose patients to acquisition of *Aspergillus* infections [58].

Despite advances in antifungal therapy, our patient-level data indicate that more than one-half of patients died with or as a

Table 5. Case-fatality rates (CFR) for patients with aspergillosis, according to type of antifungal therapy.

Antifungal therapy	No. of patients	No. of deaths	CFR, %
Amphotericin B only	559	362	64.8
Lipid formulations of amphotericin B	235	119	50.6
Oral itraconazole only	156	53	34.0
Any antifungal therapy, including multiple agents or combination therapy	1102	608	55.2
Local therapy[a]	340	82	24.1

[a] Includes treatment of aspergillosis by use of surgical procedures or other local therapies, such as percutaneous or intracavitary instillation of an antifungal agent with or without other systemic antifungal therapy.

Table 6. Type of therapy used and case-fatality rates (CFRs) for patients with aspergillosis, according to underlying condition.

Underlying condition	AmB		AmB lipid formulations		Itraconazole		AmB and itraconazole		Voriconazole or other		No therapy	
	Treated	CFR, % (no. of patients[a])	Treated	CFR, % (no. of patients[a])	Treated	CFR, % (no. of patients[a])	Treated	CFR, % (no. of patients[a])		CFR, % (no. of patients[a])	Not treated	CFR, % (no. of patients[a])
Bone marrow transplant	170 (70)	77 (81)	58 (24)	50 (2)	11 (5)	—	3 (1)	100 (3)	—	—	1 (<1)	100 (1)
Leukemia or lymphoma	227 (54)	62 (68)	120 (28)	0 (5)	41 (10)	57 (7)	23 (5)	65 (23)	5 (1)	80 (5)	7 (2)	86 (7)
Solid-organ transplant	112 (56)	92 (60)	24 (12)	79 (14)	31 (15)	50 (4)	4 (2)	— (2)	—	—	30 (15)	11 (28)
HIV	5 (29)	100 (1)	—	—	7 (41)	50 (2)	2 (12)	100 (2)	—	—	3 (18)	0 (3)

NOTE. Data are no. (%) of patients treated with a regimen, unless otherwise indicated. AmB, Amphotericin B.

[a] No. of patients is the value used as the denominator during calculation of the CFR, because treatment outcomes were not reported for all patients.

result of invasive aspergillosis, although we do not know how many of these infections were active at the time of death. The present reference-standard antifungal agent remains amphotericin B deoxycholate. However, poor tolerability often leads to use of second-line agents, such as lipid formulations of amphotericin B and itraconazole.

In our study, patients with localized infection had a considerably lower CFR than did those with disseminated disease. Mortality was high regardless of the antifungal therapy used. According to Denning [5], it has not been established whether itraconazole or the lipid preparations of amphotericin B are superior to amphotericin B. However, some patients who are refractory to, or intolerant of, amphotericin B have responded to itraconazole and lipid formulations of amphotericin B. Our data suggest that there may be a trend for lower CFRs with the use of itraconazole and lipid formulations of amphotericin B. However, patients with less severe disease were treated with itraconazole, which suggests selection bias. Also, the small numbers of patients in the non–amphotericin B treatments arms and, in one instance, the report of an open-label compassionate-use program make any interpretation difficult [44]. In a study of patients with HIV infection or AIDS, clinical failure of itraconazole was thought to reflect subtherapeutic itraconazole blood levels, which suggests the need for therapeutic drug monitoring [58]. Recently, a study that evaluated the efficacy of itraconazole against *Aspergillus fumigatus* reported a correlation between in vitro resistance and clinical failure [59]. A retrospective analysis by Stevens and Lee [44] evaluated the *Aspergillus* compassionate-use program data for itraconazole and reported a complete response of 27% and an improved response of 36%. Within the liver transplant population, one study found no differences in CFRs for patients receiving amphotericin B and liposomal amphotericin B preparations (100% vs. 89%). In this study, neither the one patient who received itraconazole alone nor the 5 patients who received combination itraconazole and amphotericin B survived [42]. In a European Organization for the Research and Treatment of Cancer multicenter prospective survey of invasive pulmonary aspergillosis among patients with hematologic malignancies, clinical outcome was improved in patients treated with combination amphotericin B and itraconazole, compared with single-agent amphotericin B, liposomal amphotericin B, or itraconazole [20]. These studies demonstrate the variable clinical response and the difficulty in enrolling patients in well-designed clinical trials.

This systematic review of the recent literature documents a persistently high CFR for invasive aspergillosis, despite the availability of newer antifungal therapies and improved management of underlying diseases and conditions. Despite increased awareness and earlier management of invasive aspergillosis, there remains a critical need for a more effective and well-tolerated antifungal agent.

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