Invasive Aspergillosis in Patients with AIDS

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The prolonged survival of profoundly immunocompromised patients with AIDS has contributed to the increasing recognition of aspergillus infections as an emerging problem. Nevertheless, many of these infections continue to be diagnosed only at autopsy. In this article we review details of 293 reported cases. Invasive aspergillosis occurs in advanced AIDS and most commonly affects the lungs, although brain involvement has also been frequently reported. The diagnosis is often difficult to make while the patient is alive, although examination of specimens obtained via bronchoalveolar lavage, percutaneous needle aspiration, or biopsy is often successful. Biopsy of the affected organ along with histologic examination and culture may be necessary for diagnosis. The dismal prognosis of invasive aspergillosis in patients with AIDS can be improved only with earlier diagnosis of disease and the availability of more-effective antifungal regimens.

Invasive aspergillosis, although typically occurring in the immunocompromised patient, has not been well recognized as an AIDS-associated condition. Yet the finding of invasive aspergillosis, even in early autopsy series of patients with AIDS, has been well documented [1–12], and the recent surge of case reports has highlighted infections due to *Aspergillus* species in these patients. This article reviews the epidemiology, clinical spectrum, diagnosis, and treatment of aspergillus infections in 293 patients positive for human immunodeficiency virus (HIV) whose cases have been described in the world literature [2–76]. (Whenever we have suspected duplication, we have attempted to exclude such cases.)

Epidemiology

Aspergillus species have a worldwide distribution, and infections in patients with AIDS have been reported from North America, Europe, Africa, and Asia. In many developing countries, cases appear to occur less frequently among these patients, either because of underdiagnosis or as a result of reduced survival. The true incidence of aspergillus infections among HIV-positive patients is difficult to estimate. Owing to the difficulty of diagnosis of clinically unsuspected disease, the diagnosis is frequently not made until autopsy. Retrospective surveys of clinically diagnosed disease have indicated an incidence of 0.9%–8.6% [14, 27, 43, 76] among patients with AIDS. A survey of 12 major autopsy series [1–12] demonstrated a prevalence of 0–12% (with an overall prevalence of 4%), although in five of these series, only neuropathological findings were reported [1–4, 9]. The diagnosis of aspergillus infection was made while the patient was alive in 169 (71%) of 239 clinical cases reported [8–13, 15–43, 46–62, 71, 73, 75]. These figures probably reflect a bias in favor of publishing reports of cases diagnosed while the patient was still alive. In our survey of five autopsy series involving 912 subjects, only 9 (22%) of the 41 reported cases of invasive aspergillosis were diagnosed antemortem [8–12]. It is thus probable that most cases remain undiagnosed (table 1).

Invasive disease appears to occur almost exclusively in patients with late- or end-stage HIV disease, occurring at a median of 10–26 months after the onset of AIDS [13, 15, 17, 30, 76]. Of the 293 reported cases, only four were classified as CDC Group II at presentation [13–14, 26, 39]. CD4 cell counts, when reported, have almost always been low ($<100/mm^3$) [13–22, 71, 76], although disease has occasionally occurred in adults with counts of $\geq 200/mm^3$ [37, 39, 69, 73–74]. Thus it is not surprising that intercurrent opportunistic pathogens are usually present, most frequently *Pneumocystis carinii* or other bacterial agents of pneumonia, as well as cytomegalovirus (CMV), *Mycobacterium avium* complex, or *Toxoplasma gondii*.

As with many other infections in advanced HIV disease, numerous risk factors for aspergillosis are postulated, but few are proven since data mostly derive from case reports. No case-control studies that assess relative risk have been published. Recognized risk factors for invasive aspergillosis in non-HIV-infected immunocompromised patients are neutropenia and prior corticosteroid or cytotoxic chemotherapy for malignant disease; the significance of administration of recently available broad-spectrum antibiotic therapy is un-

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Table 1. Prevalence of invasive aspergillosis at autospy among 1,569 patients.

Reference	No. of autopsies performed	No. of cases of aspergillosis detected	Frequency (%)
[1]	29	0*	0
[2]	153	7*	5
[3]	221	2*	1
[4]	135	1*	1
[5]	56	5	9
[6]	13	1	7
[7]	50	3	6
[8]	12	1	8
[9]	40	1*	3
[10]	101	7	7
[11]	529	26	12
[12]	230	5	2
Total number of cases	1,569	59	4

* Only neuropathological examination results reported.

certain. Neutropenia (<1,000 neutrophils × 10^6/L) was present in 92 (46%) of 202 evaluable patients with invasive aspergillosis [7, 11–44, 71, 76]; a neutrophil count of <500 × 10^6/L was documented in 6%–50% of patients in some series [13, 15, 17]. Patients may present with invasive aspergillosis even after their neutrophil counts have returned to normal (because of recovery of bone marrow from the effects of cytotoxic agents or zidovudine). Corticosteroid therapy was documented in 79 (39%) of the 202 cases; doses, where specified, were ≥10 mg of prednisolone/d or its equivalent [12, 15–16, 40–42]. Prior broad-spectrum antibiotic therapy was documented in 64 (32%) of the cases; this figure is probably underestimated. The significance of other factors is less clear. The speculation that inhalation of marijuana [13, 14] contaminated with *Aspergillus* species might constitute a risk, though intriguing, remains unproven. There are also possible links with alcohol consumption [20, 26, 27].

Among patients with invasive pulmonary aspergillosis, the apparently high frequency of preceding or intercurrent pneumonia due to *P. carinii* and other bacteria (present in 124 [73%] of 169 reported cases [7, 11–20, 22–23, 25–33, 35–36, 40, 44, 71, 75]) suggests that these infections may also be a contributary factor. However, conclusive evidence is lacking since pneumonia is a common event in patients with advanced-stage HIV disease. The development of aspergillomas in some HIV-infected patients, as is true for other groups of patients such as those with pulmonary sarcoidosis, is facilitated by existing lung damage [61, 68, 76] and has occurred within a lung cyst following pneumocystis pneumonia [57].

Some patients have no apparent risk factors for aspergillosis apart from HIV infection itself [17, 72]. Contrary to the conclusions drawn in earlier reports [7, 11], it is likely that advanced HIV infection constitutes an independent risk factor for the development of invasive aspergillosis. Alveolar macrophage function constitutes the first line of defense against *Aspergillus* conidia, and neutrophils are the major component (with some contribution from monocytes and complement activation) defending against *Aspergillus* hyphae; the function and numbers of these cells may be affected by advanced HIV infection [77]. In studies of HIV-infected children, the activity of neutrophils and peripheral blood macrophages against *Aspergillus fumigatus* was impaired [78–79], suggesting that there is increased susceptibility to infection with this organism, even if absolute numbers of cells are maintained.

Aspergilli are common environmental saprophytes, accounting for up to 40% of the fungal flora in hospital and home environments. Many nosocomial outbreaks in other groups have been described (e.g., bone marrow transplant recipients). A cluster of seven cases occurring on an AIDS ward has been described [36]; nosocomial spread was suspected but remains unproven.

In some of the reports surveyed, no details were available on the species of *Aspergillus* isolated. In others, the diagnosis was made histologically. While it may be difficult to differentiate *Aspergillus* hyphae from those of other pathogenic molds, we consider the overwhelming majority of these cases do indeed represent aspergillosis. The most common species causing disease in patients with AIDS is *A. fumigatus*, which represented 73 (84%) of 87 isolates recovered [12, 13, 15–17, 20, 23–24, 26, 29–30, 33–34, 36–37, 39–40, 42, 48–49, 52, 54, 57, 68–71, 73–75]. *Aspergillus flavus* was identified in 7 cases (8%), *Aspergillus niger* in 4 (5%), and *Aspergillus terreus* in 3 (3%) [12, 15–17, 40, 53, 62, 69, 75].

Clinical Syndromes

Table 2 lists the major sites of infection. The lung is the organ most frequently involved (>70% of cases); brain involvement was reported in 10% of cases. Disease is almost always invasive, although aspergillus bronchitis and aspergillomas have been reported. Whether or not there is increased risk of allergic disease, such as allergic bronchopulmonary aspergillosis or allergic aspergillus sinusitis, is unknown.

The diagnosis of infection while the patient is alive is often possible only with culture and/or histologic examination of a biopsy specimen from the affected organ. Results of blood cultures, although only rarely positive [80], should suggest the possibility of disseminated disease [20], fungal endocarditis or myocarditis [37], mycotic aneurysm, or an infected central venous catheter. Precipitins (*Aspergillus*-specific IgG) are elevated only in patients with aspergilloma [61]. In other groups of immunosuppressed patients, *Aspergillus* antigen in blood or urine may be detected occasionally [81], but in general, serology is unhelpful.

Table 2. Sites of aspergillosis in 293 cases among HIV-positive patients.

Site/infection	No. of patients (%) with indicated infection	References
Respiratory tract*		
Sinusitis	9 (3)	[13, 15, 17, 24, 33, 41, 53, 62, 67]
Otomastoiditis	5 (2)	[17, 48, 56]
Laryngitis	2 (<1)	[23, 33]
Tracheobronchitis	11 (4)	[13, 17, 30, 53, 71–72]
Obstructing bronchial aspergillosis	5 (2)	[13, 32, 39]
Invasive pulmonary aspergillosis	208 (71)	[7, 9, 11–23, 25–32, 35, 36, 40, 43, 46, 50–53, 58, 59, 63, 66, 69, 70, 74–76]
Empyema/pleural mass	5 (2)	[13, 30, 36, 69]
Aspergilloma	4 (1)	[57, 61, 68, 76]
CNS*		
Brain†	30 (10)	[2–4, 9, 11, 13, 15, 17, 26, 30, 43–44, 51–52, 54, 60, 64, 67, 69–70, 75]
Other systems*		
Cardiac	10 (3)	[15, 17, 28, 29, 31, 44, 54, 67, 69]
Renal	12 (4)	[11, 15, 17, 18, 31, 34, 49, 54, 66, 69]
Thyroid	4 (1)	[11, 31]
Other*: spleen (3), musculoskeletal (3), lymph node (2), pancreas (2), liver (2), mouth, palate, adrenal, epididymis, gastrointestinal, skin	16 (5)	[8, 13, 17, 18, 20, 23, 30, 36, 38, 42, 47, 54, 55, 71, 73]
Two or more organs involved	47 (16)	[4, 10–11, 13, 15–18, 20, 23, 26, 28, 29, 32, 33, 36, 41, 44, 51–54, 69, 73]
Site of disease not specified	13 (4)	[3, 45, 64]

* Includes disease occurring in more than one site.
† Including spinal cord involvement in one patient.

Respiratory tract infections. Invasive pulmonary disease presented most frequently as cough (92%), fever (91%), dyspnea (65%), chest pain (24%), and hemoptysis (9%) in our survey of 78 evaluable patients [13, 17–19, 26, 31, 32, 35, 40, 46, 69]. There is often a prior history of pneumonia due to *Pneumocystis* or other bacteria or CMV. The chest radiograph almost always shows abnormalities, but appearances may be variable. They include localized or diffuse infiltrates and nodules. Cavitary lesions with thick or thin walls are relatively distinctive. They are usually present in the upper lobes (figure 1) and may be confused with those of tuberculosis. Pleural effusions may occasionally be present; two cases of empyema due to *Aspergillus* species have been reported [36, 69].

The diagnosis of invasive pulmonary aspergillosis can be difficult. *Aspergillus* species may be present in the respiratory tract as commensals in both healthy individuals and the immunocompromised [82], including ~4% of patients with AIDS [12, 83–84]. Thus, the isolation of *Aspergillus* species from respiratory secretions does not automatically imply invasive disease. However, studies of bone marrow transplant recipients as well as of those with a hematologic malignancy have shown that positive sputum culture is strongly predictive of invasive disease [82, 85]. The presence of *Aspergillus* species in the sputum of immunocompromised patients, including those with AIDS, in association with abnormal findings on a chest radiograph should suggest the possibility of invasive pulmonary aspergillosis [12]. The converse is not true: a negative sputum culture does not exclude the possibility of aspergillosis. Bronchoscopic findings may appear to be normal, but lavage usually yields the organism [17]. Transbronchial biopsy (although often unrewarding) and transthoracic needle aspiration of localized lesions may also clinch the diagnosis [13].

The three patients with aspergilloma who have been described all had existing lung damage (one had aspergilloma within a cyst that had resulted from pneumocystis pneumonia). Characteristic changes were seen on radiographs and computed tomographic (CT) scans of the thorax. Hemoptysis may be fatal [68] and require surgical intervention. Ulcerative or pseudomembraneous tracheobronchitis caused by *Aspergillus* species is a recently described entity occurring in immunocompromised patients who do not have AIDS [86–87] and has been reported in 11 patients with AIDS [13, 17, 30, 71–72]. Patients present with dyspnea and wheezing (which may mimic asthma); fever and a cough (or hemoptysis) may also be present. Bronchoscopy reveals ulcerative lesions or fungal necrotic pseudomembranes [13, 17] that

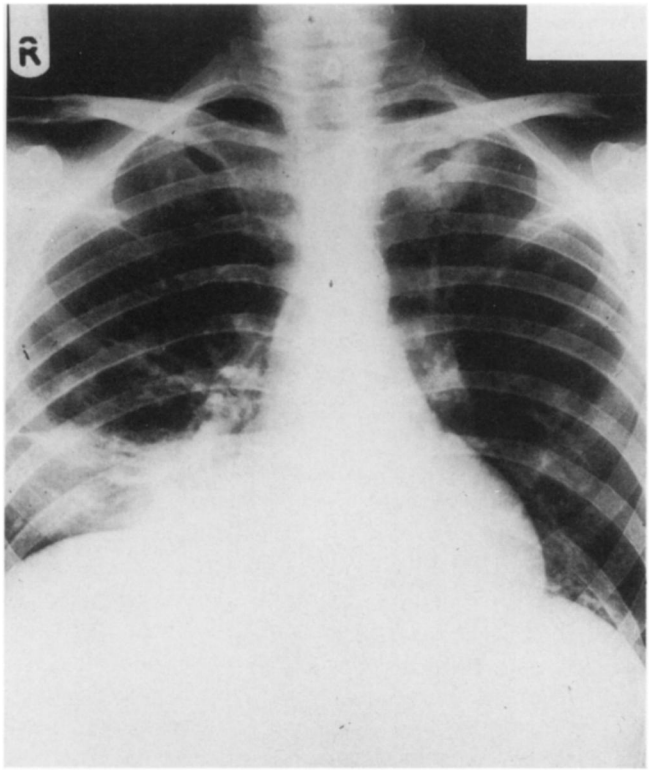

Figure 1. Finding of pulmonary aspergillosis in a patient who had AIDS for 3 years (CD4 count, $>10/mm^3$). Right middle-lobe consolidation and a left upper-lobe cavity as seen in a previously normal lung; the diagnosis was made by culture of a bronchoalveolar lavage specimen and was confirmed at autopsy.

may be extensive and invade peribronchial tissue and local blood vessels, resulting in distant spread of disease. Associated lung parenchymal disease is found in 50% of cases, and distant dissemination is found in 25% of cases [71].

A noninvasive form of airway disease, called obstructing bronchial aspergillosis, has also been described in patients with AIDS [13, 32, 39]; a similar case occurred in a bone marrow transplant recipient [88]. Symptoms are cough, fever, wheezing, hemoptysis, and hypoxemia. The distinctive feature is that large mucoid casts full of *Aspergillus* organisms are expectorated spontaneously or are encountered at bronchoscopy. These casts plug the airways and may result in segmental or lobar atelectasis, usually affecting the lower lobes. There is little or no bronchial inflammation in the early stages. Chest radiographs show bilateral lower-lobe or generalized hazy shadowing. Disease may become invasive and extend upwards to produce pseudomembraneous tracheobronchitis, particularly if the disease is left untreated [13]. The diagnosis of aspergillus tracheobronchitis and obstructing bronchial aspergillosis is established at bronchoscopy.

The larynx was the site of disease in two patients [23, 33] who presented with hoarseness and/or aphonia. The diagnosis was made by direct laryngoscopy or bronchoscopy and was confirmed by histologic and microbiological examination of biopsy material. In laryngeal aspergillosis the cords become thickened and may be destroyed or covered by an extensive membrane.

Nine cases of aspergillosis of the sinuses in patients with AIDS have been reported; the patients usually presented with nasal discharge and facial pain. These were all invasive infections, sometimes penetrating into adjacent tissue such as the orbit and brain [24, 41, 67]. The sphenoid sinuses have also been affected (figure 2) Diagnosis is made by culture and/or biopsy, and in addition to specific antifungal chemotherapy, surgical debridement may be necessary to control disease.

Invasive otomastoiditis (invasive external otitis) typically presents as ear pain (often severe) and otorrhea; auriscopic examination reveals a perforated tympanic membrane [17, 48, 56]. The mastoid air cells are usually involved, but CT scans of the affected area do not always reveal abnormality. Facial nerve involvement has been documented. Culture is mandatory, since other organisms (including fungi such as *Pseudallescheria*) are also recognized causes of disease.

CNS infections. All too often CNS involvement is documented only at autopsy. CNS disease often takes the form of cerebral infarction, hemorrhage, or abscess formation; the patient presents with fever and seizures or symptoms mimicking those associated with stroke or a space-occupying lesion. Spinal cord involvement and chronic meningitis have been documented [69]. A CT scan of the head may show single or multiple nonenhancing lesions, often with surrounding edema; in addition there may be bony invasion [69, 75]. Examination of a CSF sample is usually unhelpful. The diagnosis is difficult to make since diverse pathology produces

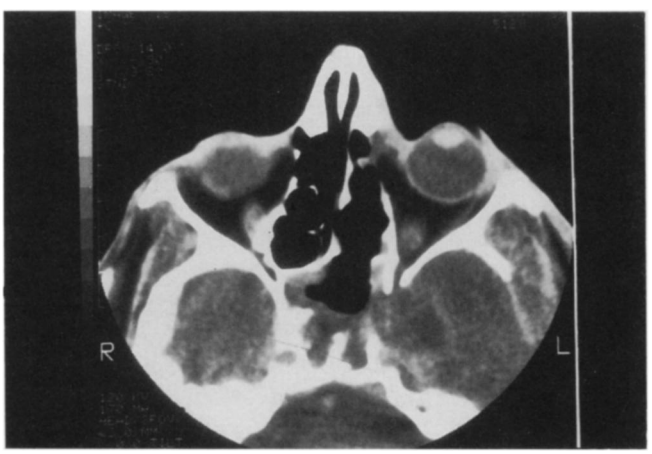

Figure 2. CT scan showing sphenoid sinus aspergillosis with destruction of the lateral wall of the sinus and temporal lobe extension. The patient had suffered from chronic headaches for 4 months; the diagnosis was made by culture of *A. fumigatus* from a percutaneous aspirate obtained through a burr hole and was confirmed at autopsy.

similar symptoms and signs in patients with AIDS. The possibility of cerebral infection is suggested by the presence of concurrent invasive pulmonary aspergillosis. If the diagnosis is in doubt, biopsy or aspiration of a localized lesion should be considered.

Cardiac aspergillosis. Cardiac involvement usually takes the form of endocarditis or myocarditis, manifesting as fever, cerebral embolic disease, cardiac failure, and conduction defects such as arrhythmias and atrioventricular block. The diagnosis is seldom made while the patient is alive. Positive results of fungal blood cultures should alert the clinician [37], and echocardiography may reveal vegetations [28]. Hematogenous dissemination will often result in involvement of other organs, predominantly the lung and brain.

Other sites. Renal aspergillosis has been described. This may take the form of invasive disease (presenting as fever, loin pain, renal dysfunction, hematuria, and pyuria [17, 18, 49]) or fungal balls [34]; surgical intervention (nephrectomy or drainage) may be required to relieve obstruction or remove infected tissue [49, 66]. A number of other organs have been infected, including the liver [47, 73] and spleen [7, 54, 73] (complicated by chylous ascites [73]), as well as the palate and mouth [18, 55], adrenal glands [23], and thyroid [11, 31]. There have also been single case reports of infection occurring in peripancreatic tissue [38], skin [8], epididymis [36], muscle [42], and prepatellar panniculitis [30]. There are no particularly distinctive clinical features, and biopsy or aspiration of the affected organ is necessary for diagnosis.

Disseminated disease affecting two or more organs is relatively common (it is present in at least 16% of cases). Again, the lungs are most frequently involved.

Antifungal Therapy

The response to antifungal chemotherapy of AIDS patients with invasive aspergillosis is considerably inferior to that observed in patients who do not have AIDS. This finding probably reflects the advanced stage of underlying disease and the presence of intercurrent illness due to other opportunistic pathogens or tumors. Amphotericin B with or without flucytosine has been used with varying success [13, 18, 57, 89]. Although the optimal dose has yet to be defined, we suggest starting with 0.8–1.0 mg/(kg · d) and titrating the dose according to response or evidence of toxicity. The role of liposomal preparations (e.g., AmBisome; Vestar, San Dimas, CA) is even less certain, but they may be considered in cases of drug intolerance. Higher doses can and should be given (e.g., 1–4 mg/(kg · d) for invasive aspergillosis [90]. The effectiveness of amphotericin B may be limited by its toxicity as well as the associated hazards and inconvenience of long-term intravenous infusions, since lifelong therapy is usually indicated.

Response to amphotericin B therapy may be inferior to that observed when itraconazole is given with or without flucytosine [21, 24]. If itraconazole is used, loading doses (e.g., 600 mg/d for 4 days) should be given, followed by maintenance with at least 400 mg/d administered with food. Therapy should be continued indefinitely. However, absorption of itraconazole may be impaired, and it often interacts with other drugs (particularly inducers of the p450 enzymes, such as rifampin). Serum concentrations of itraconazole should be measured to ensure absorption and to monitor levels, particularly if there are interactions accelerating its metabolism. While response to itraconazole therapy has been observed in a few patients [21–33], in many others there is neither dramatic response nor deterioration, and 25%–35% of patients may remain stable for some weeks before therapy subsequently fails or they die of another AIDS-related problem [24]. Thus, the general outlook is dismal; death occurs at a median of 2–4 months after diagnosis [13, 14, 17, 18, 23], reflecting in part the advanced stage of AIDS. Even if control of disease is successful (sustained in a minority of patients for >12 months), recrudescence is common. Hemoptysis is also a frequent fatal event in patients who have cavitary disease [13, 76]. Given the limited success with current antifungal agents, the use of newer agents as experimental therapy is appropriate for those in whom conventional treatment has failed.

Patients with obstructing bronchial aspergillosis generally respond to therapy with itraconazole [13], which may prevent progression to pseudomembranous aspergillar tracheobronchitis. Bronchoscopy may be both diagnostic and therapeutic in these individuals, especially when there is atelectasis due to obstructing fungal plugs.

Prophylaxis

Should antifungal prophylaxis be considered and, if so, for whom? This issue remains unresolved. The decision to embark upon prophylaxis for aspergillosis in a patient with AIDS is influenced by the likelihood of disease and the effectiveness of the agent used; data on both are lacking. Although advanced HIV infection itself constitutes a risk factor, most individuals with low CD4 cell counts will not develop aspergillosis, and the cost-benefit ratio needs to be carefully evaluated, especially as therapy may be lifelong. A better option might be to target the highest risk groups; these would include patients with low CD4 cell counts who have *Aspergillus* species isolated from sputum and may also include those with neutropenia or who are receiving corticosteroid therapy. It is also unclear which drug or dose should be recommended for this purpose. The only effective oral agent presently available is itraconazole, which also has activity against species of *Candida*, *Histoplasma*, and *Cryptococcus*. However, its use in this context has not been studied and cannot be recommended at present.

Despite recent advances in antifungal therapy, the mortality associated with invasive aspergillosis remains high, even

when the infection is treated aggressively. There is clearly an urgent need for earlier diagnosis and improved drug therapy for invasive aspergillosis in patients with AIDS.

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