MAJOR ARTICLE

Comparison of Epidemiological, Clinical, and Biological Features of Invasive Aspergillosis in Neutropenic and Nonneutropenic Patients: A 6-Year Survey

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Background. Invasive aspergillosis is an opportunistic infection that occurs mainly among patients with prolonged neutropenia. Few data are available on invasive aspergillosis in nonneutropenic patients.

Methods. The aim of this survey was to compare neutropenic and nonneutropenic patients who had received a diagnosis of invasive aspergillosis at our institution during a 6-year period.

Results. Among the 88 cases of invasive aspergillosis analyzed here, 12 were histologically proven, 52 were probable, and 24 were possible. Forty-seven percent of cases were diagnosed in the intensive care unit, and 40% were diagnosed in hematology units. Neutropenia was a risk factor for 52 patients (59%), most of whom had hematological or solid malignancies. Among the 36 nonneutropenic patients (41%), the main underlying conditions were steroid-treated chronic obstructive pulmonary disease, asthma, rheumatoid arthritis, giant-cell arteritis, and microvascular disorders; 10 patients were recipients of solid-organ transplants, and 1 patient was seropositive for human immunodeficiency virus. The distribution of proven and probable invasive aspergillosis was similar for neutropenic and nonneutropenic patients. The mortality rate was 71.5% overall and was significantly higher among nonneutropenic patients than among neutropenic patients (89% vs. 60%; $P < .05$). Compared with neutropenic patients, nonneutropenic patients were significantly less likely to have symptoms of invasive aspergillosis and more likely to have frequent intercurrent pneumonia due to another microorganism. The sensitivity of mycological examination of bronchoalveolar lavage fluid specimens was higher for nonneutropenic patients than for neutropenic patients (85% vs. 58%; $P < .05$), whereas the sensitivity of antigenemia was the same for the 2 populations (65% vs. 64%). Findings on thoracic computed tomographs were similar, except that segmental areas of consolidation occurred more frequently among neutropenic patients.

Conclusion. This survey at a whole institution underlines the high number of cases of invasive aspergillosis among nonneutropenic patients, with an overall mortality rate that was significantly higher than that for neutropenic patients.

Invasive aspergillosis (IA) is an opportunistic infection that occurs mainly among patients with prolonged neutropenia [1–4]. The mortality rate exceeds 50% and can reach 90% in allogeneic hematopoietic stem cell transplant recipients [5–8]. During the 1990s, the management of IA in neutropenic patients improved with the advent of new diagnostic tools and new antifungal drugs. Early CT and regular screening for *Aspergillus* galactomannan antigen or DNA in serum samples are particularly important for successful management of IA [3, 9–12].

Few data are available on IA in allogeneic hematopoietic stem cell transplant recipients after recovery from neutropenia [13] or in patients who are free of hematological disorders and malignancies. However, IA can also occur after solid-organ transplantation and during long-term corticosteroid therapy [8, 14], and it is an emerging opportunistic infection in patients with

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chronic respiratory diseases and in patients who are receiving immunosuppressive therapies [15–24]. Paterson [25] recently reviewed the clinical features of IA in nonconventional hosts, but there are no studies comparing neutropenic patients with IA and nonneutropenic patients with IA. Aspergillosis is perceived as less of a concern in the latter population; therefore, it tends to be diagnosed at a more advanced stage, at which point even new antifungals have poor efficacy.

The original aim of this study was to characterize all patients who received a diagnosis of IA at our institution. However, the large proportion of nonneutropenic patients with IA gave us the opportunity to compare the diagnosis and therapeutic management of these patients with those for neutropenic patients.

PATIENTS AND METHODS

Setting. Rennes University Hospital, a 1978-bed institution, is a regional center for hematology, bone marrow and solid-organ transplantation, and cardiopneumology. Adult and pediatric hematology units are equipped with a laminar air-flow system with high-efficiency particulate air filters (HEPA filter class 14 to provide an overall efficiency of at least 99.995% for particles between 0.3 μm and 3.0 μm) in 10 and 4 patient rooms, respectively. Regular environmental surveys are conducted, and these include surveys for fungal contamination.

Patients and study design. This survey covered a 6-year period: a retrospective study for the period from 1 January 1998 through 31 December 1999 and a prospective study for the period from 1 January 2000 through 31 December 2003. During the retrospective study, patients were identified from a variety of sources, including archives, mycology listings, histopathology reports, and individual physicians. For the prospective survey, an institutional aspergillosis study group was set up in 2000. Case notifications were prospectively recorded for all patients in the entire hospital who received a diagnosis of IA by trained physicians and from mycology and radiology listings and histopathology reports.

Case definition of nosocomial IA. Cases of IA were classified as possible, probable, or proven on the basis of the classification system of the European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) [26]. Invasive nosocomial aspergillosis is not yet clearly defined in the literature. Acquisition of IA was considered to have been nosocomial if the patient had a respiratory sample culture result and/or a histopathology report consistent with IA and/or 2 positive *Aspergillus* galactomannan (GM) antigenemia tests $\geqslant$7 days after hospital admission; other cases were considered to have been community acquired. Cases were considered to be indeterminate when the diagnosis was made at autopsy or when the findings of biological investigations were normal.

Diagnostic methods. All clinical samples were examined microscopically (using pellets and smears) after May-Grünwald Giemsa and Gomori-Grocott staining. All samples were cultured on Sabouraud dextrose agar at 37°C for 7 days.

Aspergillus GM antigenemia was detected using an ELISA (Platelia *Aspergillus;* Bio-Rad) after January 2000. The positivity cutoff value was 1.5, as recommended by the manufacturer in the European Union. Two positive GM test results were required for confirmation, in accordance with international consensus criteria [26]. Samples that yielded positive results in which chemical interference was known to have occurred were excluded [27].

Two different methods were used for detection of anti-*Aspergillus* antibody: immunoelectrophoresis (Antigens *Aspergillus* and Control *Aspergillus;* Bio-Rad) and either electrosyneresis/the Ouchterlony method (Antigens *Aspergillus* and Control *Aspergillus;* Bio-Rad) or ELISA EIA IgG *Aspergillus fumigatus* (Virion-AES Laboratoire) before and after 2000, respectively. Patients underwent regular imaging studies (standard radiography and high-resolution CT).

Statistical analysis. We performed univariate statistical analysis using EpiInfo software, version 6.0 (Centers for Disease Control and Prevention), with the χ^2 test and Fisher's exact test used for qualitative variables and Student's *t* test used for quantitative variables. Multivariate analysis of prognostic factors using logistic regression was performed with SPSS software for Windows, version 12.0 (SPSS). *P* values $<.05$ were considered to be statistically significant.

RESULTS

Patients and Underlying Diseases

Eighty-eight patients were enrolled during the 6-year study period, with a mean number of 14–15 patients per year. Twelve cases (14%) were histologically proven, 52 (59%) were probable, and 24 (27%) were possible.

The ratio of male to female patients was 1.6:1. The mean age of the patients was 52 years (range, 4–89 years). Most patients (58%) were aged 40–69 years; 9% were $\leqslant$19 years of age, 16% were 20–39 years of age, and 17% were >70 years of age. Cases of IA were diagnosed mainly in the intensive care unit (47% of cases) and the hematology unit (40% of cases overall [33% of cases in adults and 7% of cases in children]) (figure 1).

The patients' underlying diseases are shown in figure 2. As expected, hematological malignancies were the leading underlying diseases for 49 patients. Acute leukemia was the main hematological malignancy (26 patients). Six other patients underwent bone marrow transplantation (3 received allogeneic stem cell grafts and 3 received autologous stem cell grafts).

Chronic pulmonary disease was present in 17 patients, most of whom had steroid-treated chronic obstructive pulmonary disease (COPD) and asthma. In patients with COPD, only acute forms of IA were included in the analysis. Ten patients were

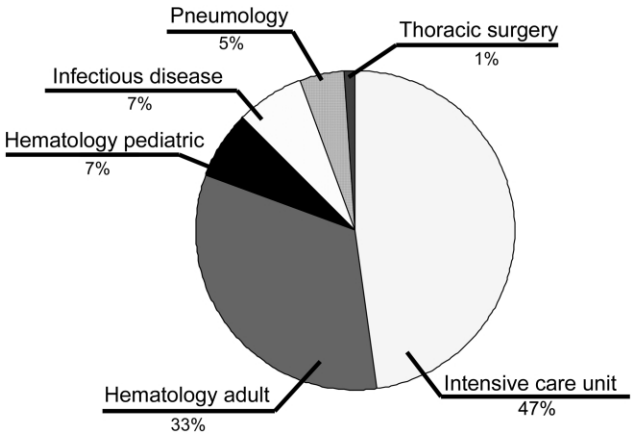

Figure 1. Distribution of invasive aspergillosis cases, by hospital ward.

solid-organ transplant recipients (5 received liver transplants, 3 received heart transplants, and 2 received renal grafts), 6 patients had systemic diseases (rheumatoid arthritis, giant cell arteritis, and vasculitis disease) that were treated with immunosuppressive drugs, and 3 patients had solid tumors. Only 1 of the 88 patients was infected with HIV.

Risk factors are listed in figure 3. Neutropenia (polymorphonuclear neutrophil count, <0.5 G/L) during the previous 15 days was a major risk factor (59% of patients). Among patients with hematological malignancies, 6 were not neutropenic at the time of IA, 1 of whom received an allogeneic hematopoietic stem cell transplant and developed an IA after recovery from neutropenia. The mean duration of neutropenia was 30 days (range, 3–120 days), and the median duration was 12 days. Broad-spectrum antibacterial agents and corticosteroids were administered to 90% and 89% of the patients, respectively, and cytotoxic chemotherapy and other immunosuppressive therapies (i.e., cyclosporine, tacrolimus, methotrexate, ciclophosphamide, and azathioprine) were administered to 55% and 22% of patients, respectively. A total of 12.5% of patients had previously been colonized ($n = 8$) or infected ($n = 3$) with *Aspergillus* species, and 10% of patients were coinfected with cytomegalovirus ($n = 6$), *Pneumocystis jiroveci* ($n = 2$), or both ($n = 1$). The main reasons for hospitalization were respiratory failure and receipt of first-line treatment (usually cytotoxic chemotherapy) for an underlying disease.

Clinical Signs and Nosocomial Acquisition of IA

The lung was the most common site of infection (96.5% of cases). Most patients developed pneumonia and prolonged fever that did not respond to broad-spectrum antibacterial therapy (figure 4). Fever was present in 85% of patients, and all but 4 patients had at least 1 clinical sign of IA, consisting of dyspnea (65%), cough (51%), chest pain (24%), and/or hemoptysis (7%). Cutaneous lesions were observed in 8% of cases (1 case of primary cutaneous IA, 3 secondary cutaneous sites of infection, and 3 cutaneous lesions with negative *Aspergillus* culture results). Neurologic disorders were present in 17% of cases and in 5 of 15 patients with proven secondary cerebral IA. Three patients had another suspected secondary site of IA (i.e., kidney, pericardium, and endocardium). Two patients were asymptomatic.

IA was diagnosed a median of 18.5 days after hospital admission (mean time to diagnosis, 24 days). IA was nosocomial in 55 cases (62.5%) and indeterminate or community acquired in 18 cases (20.5%) and 15 cases (17%), respectively.

Diagnostic Methods

Mycological examination. Seventy-nine patients (90%) underwent at least 1 mycological examination, with positive results in 76% of patients. Direct examination and/or culture of bronchoalveolar lavage (BAL) fluid specimens yielded positive results for 46 of 67 patients (sensitivity, 69%). The sensitivity reached 83% for proven and probable IA. The diagnostic yield of mycological examination of BAL fluid specimens, according to case classification, is shown in table 1. Seven patients underwent a skin biopsy, and direct examination and/or culture of the skin biopsy specimens yielded positive results for 4 patients. Invasive procedures, such as lung biopsy or pulmonary resection, were performed for 6 patients, and results of tests were positive for 4. Blood culture results were never positive. *A. fumigatus* was the species most frequently recovered by culture (44 patients [90%]), either alone or with another *Aspergillus* species, followed by *Aspergillus terreus* (4 patients [8%]), *Aspergillus nidulans* (1 patient [2%]), *Aspergillus niger* (1 patient [2%]), and *Aspergillus flavus* (1 patient [2%]).

Aspergillus *GM antigenemia.* Forty-six of 88 patients were tested for *Aspergillus* GM antigenemia. Among the 34 patients who underwent regular monitoring for *Aspergillus* GM anti-

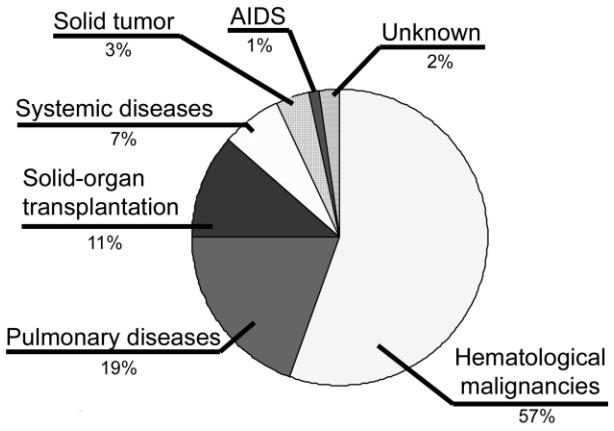

Figure 2. Underlying diseases and risk factors present in patients with invasive aspergillosis.

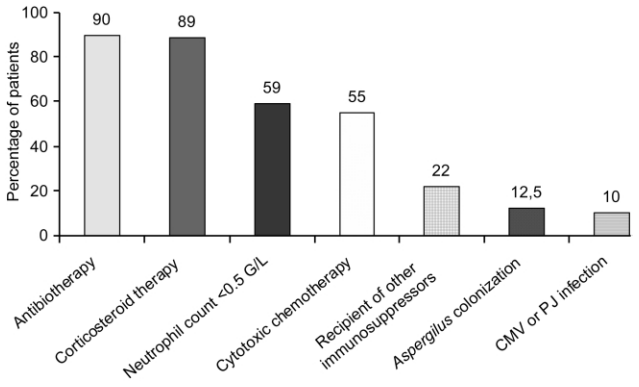

Figure 3. Risk factors for invasive aspergillosis. CMV, cytomegalovirus; PJ, *Pneumocystis jiroveci.*

genemia, as recommended [2], the sensitivity was 65% overall (22 of 34 patients; 4 [100%] of 4 patients with proven IA and 17 [85%] of 20 patients with probable IA); it was 87.5% (21 of 25 patients) for cases of proven and probable IA, and 10% (1 of 10 patients) for cases of possible IA. For 13 of 22 patients who had positive results of tests during regular monitoring, antigenemia was the test that revealed the diagnosis. The *Aspergillus* GM antigenemia test yielded positive results before mycological tests in 17 of 22 cases.

Anti-*Aspergillus *antibody detection. Thirty-seven patients (42%) had at least 1 antibody test, the result of which was positive in 30% of cases. This test was used more often in nonneutropenic patients (58% versus 31% in severe neutropenic patients). In these nonneutropenic patients the sensitivity of antibody testing was 48%, compared with only 6% in patients with severe neutropenia.

Histological examination. Autopsy was performed for 8 (13%) of the 63 patients who died. Postmortem diagnosis was made in 4 cases. Autopsy confirmed the diagnosis in 2 cases (1 case of histologically proven IA that had been diagnosed by skin biopsy, and 1 case of pulmonary IA that had been considered probable before death). In the other 2 cases (which were cases of probable IA), autopsy findings were noncontributory.

Imaging. Chest radiographs generally showed nonspecific infiltrates (alveolar syndrome, in 28 patients; interstitial syndrome, in 23; nodules, in 18; and cavitated nodules, in 3). Typical lesions, such as cavitated nodules, were occasionally observed.

High-resolution CT was performed for 66 patients (75%) an average of 6 days after the onset of symptoms (range, 24 days before to 35 days after the onset of symptoms). The principal findings were segmental areas of consolidation or wedge-shaped consolidation (53% of patients), nodule(s) (44%) or nodular lesions with cavitation (21%), ground-glass attenuation (30%), and pleural effusion (36%). More specific signs, such as nodular lesions with halo sign or air crescent sign, were less common (6% and 18% of patients, respectively).

Treatment

Lobectomy or wedge resection, in addition to administration of antifungal therapy, was performed in 3 pediatric patients, with no surgical complications (figure 5). Two of these patients underwent additional immunosuppressive treatment without recurrence or relapse of aspergillosis, and 1 patient died of progression of an underlying disease.

Therapeutic management changed radically during the study period. First-line treatment gradually changed from deoxycholate amphotericin B (66.6% of patients during the period of 1998–2001) to voriconazole (74.2% of patients during the period of 2001–2003). Second-line treatments now include lipid formulations of amphotericin B and caspofungin acetate. Despite these changes, no significant statistical difference in the mortality rate by year was observed.

Deoxycholate amphotericin B and voriconazole were the 2 drugs used for empirical therapy. Itraconazole was mainly used as a second-line treatment.

Outcome and Prognostic Factors

Six patients were lost to follow-up (table 2). Despite treatment, the overall crude mortality rate among patients for whom outcome data were available was 76.8% (63 of 82 patients). Nineteen patients recovered from IA with receipt of antifungal therapy. The mortality rate was higher among patients with proven IA. No significant difference of mortality rate was observed between female and male patients (59% vs. 80%). The mortality rates among patients with hematological malignancies and solid tumors were 64.4% and 66.6%, respectively, compared with 94% for nonneutropenic patients. Fungal disease was considered to be the immediate cause of or a significant contributory factor in death for 17 patients (27%; 9 and 8 deaths among neutropenic and nonneutropenic patients, respectively).

The following potential prognostic factors were examined

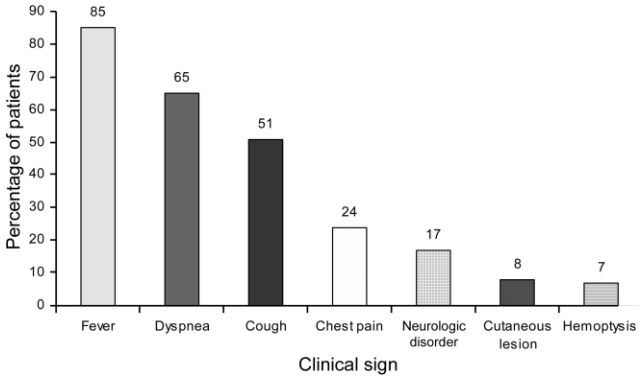

Figure 4. Clinical signs of invasive aspergillosis

more closely: disseminated fungal disease, bilateral pulmonary disease, the duration of neutropenia, intercurrent infection with *P. jiroveci* and/or cytomegalovirus, intercurrent bacterial pneumonia, the time from diagnosis to treatment outset, and the presence of anti-*Aspergillus* antibodies. Three factors were associated with a poor prognosis: (1) disseminated disease was associated with a 100% mortality rate (6 of 6 patients died), (2) coinfection with *P. jiroveci* and/or cytomegalovirus was associated with a mortality rate of 78% (7 of 9 patients), and (3) intercurrent bacterial pneumonia was associated with a mortality rate of 78.5% (22 of 28 patients).

Comparison of Neutropenic and Nonneutropenic Patients with Regard to Epidemiological, Clinical, and Biological Features

There was no significant difference in the ratio of male to female patients between the 2 groups. The distribution of proven, probable, and possible cases of IA was also similar (table 3). Among the significant differences, IA was less symptomatic (particularly with regard to fever, cough, and chest pain), was more frequently associated with pneumonia due to another microorganism, and was more frequently fatal in nonneutropenic patients than in neutropenic patients. The only significant difference in thoracic CT findings was that segmental areas of consolidation were more common in neutropenic patients. The sensitivity of mycological examination of BAL fluid specimens and antibody serologic testing was higher for nonneutropenic patients, whereas *Aspergillus* GM antigenemia testing was similarly sensitive in the 2 populations. Multivariate analysis of prognostic factors showed that only nonneutropenic status was associated with a lower mortality rate (OR, 0.182; 95% CI, 0.048–0.686; $P < .001$).

DISCUSSION

The incidence of IA is probably underestimated, owing to the poor sensitivity of clinical and radiological investigations and diagnostic tests [2, 28]. In addition, large surveillance programs mainly focus on hematology and oncology patients. However, an increasing number of reports underline the susceptibility of nonneutropenic patients to invasive fungal infections [13, 15–24, 29, 30]. In particular, Meersseman et al. [20] recently reported the findings of a retrospective study of 69 cases of IA in patients without malignancies who were hospitalized in a medical intensive care unit.

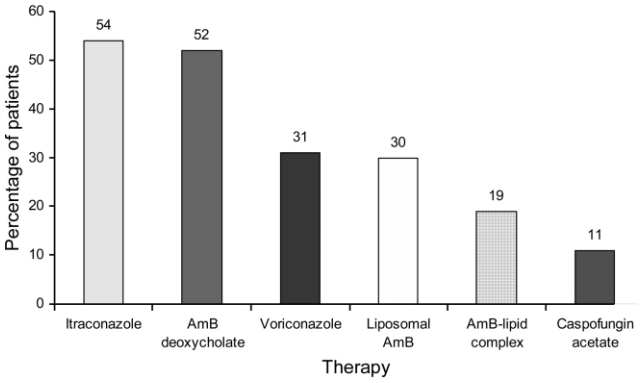

Figure 5. Medical treatments received by patients. AmB, amphotericin B.

During our 6-year study, we analyzed the epidemiology of IA in our institution, first retrospectively and then prospectively. We created an aspergillosis study group composed of specifically trained physicians, radiologists, pathologists, chemists, and mycologists, to improve the case identification rate. In each case, IA was classified as possible, probable, or proven on the basis of EORTC/MSG criteria [26]. To our knowledge, this is the first survey of all-comer patients at a single institution.

We observed a high frequency of IA in nonneutropenic patients who had been hospitalized for such underlying diseases as COPD, asthma, rhumatoid polyarthritis, giant cell arteritis, and vasculitis. Receipt of high-dose or continuous corticosteroid therapy was the only identified risk factor for 19 such patients (22%). Low steroid doses (<15 mg of prednisone per day or equivalent) are sufficient for IA to develop when the medication is administered continuously, as confirmed in a report by Rello et al. [31]. In these moderately immunosuppressed patients, *Aspergillus* colonization may contribute to the onset of IA, particularly in patients with chronic pulmonary disease. It is noteworthy that 3 *Aspergillus*-colonized patients with COPD developed acute IA in the absence of corticosteroid therapy. The higher prevalence of IA among male patients is

Table 1. Results of mycological examination of bronchoalveolar lavage fluid specimens, according to the case classification of invasive aspergillosis (IA).

	No. (%) of patients			
Result	Proven IA ($n = 4$)	Probable IA ($n = 43$)	Possible IA ($n = 20$)	Total ($n = 67$)
Positive result of DE	1 (25)	24 (56)	5 (25)	30 (45)
Positive culture result	2 (50)	32 (74)	3 (15)	37 (55)
Positive result of DE and/or culture	2 (50)	37 (86)	7 (35)	46 (69)

NOTE. DE, direct examination.

Table 2. Outcome of invasive aspergillosis (IA), according to the patient's underlying disease and case classification.

Primary disease/underlying condition and case classification	No. (%) of patients, by outcome		
	Death (n = 63)	Recovery (n = 19)	Unknown (n = 6)
Primary disease/underlying condition			
Hematological malignancy			
All (n = 49)	29 (59)	16 (33)	4 (8)
Acute leukemia (n = 19)	8 (42)	11 (58)	0 (0)
Other hemopathy (n = 30)	21 (70)	5 (17)	4 (13)
Solid-organ transplantation (n = 10)	9 (90)	1 (10)	0 (0)
Chronic pulmonary disease (n = 18)	16 (89)	1 (5.5)	1 (5.5)
Vasculitis disease (n = 5)	5 (100)	0 (0)	0 (0)
Solid tumor (n = 3)	2 (67)	0 (0)	1 (33)
AIDS (n = 1)	1 (100)	0 (0)	0 (0)
Unknown (n = 2)	1 (50)	1 (50)	0 (0)
Case classification			
Proven IA (n = 12)	10 (83)	2 (17)	0 (0)
Probable IA (n = 52)	37 (71)	10 (19)	5 (10)
Possible IA (n = 24)	16 (67)	7 (29)	1 (4)
All cases of IA (n = 88)	63 (71.5)	19 (21.5)	6 (7)

consistent with the predominance of underlying pulmonary diseases among male subjects [7]. Solid-organ transplantation was the underlying risk factor for 10 patients, one-half of whom underwent liver transplantation. It should be noted that lung transplantation is not performed in our institution.

Interestingly, the distribution of proven plus probable IA did not differ between neutropenic and nonneutropenic patients in this study (75% and 69%, respectively; $P = .77$). This is in keeping with the findings of a retrospective study by Meersseman et al. [20], who reported 75% proven plus probable IA among all patients diagnosed with IA. IA in nonneutropenic patients is of special concern, with a mortality rate of 89% in our study, compared with a rate of 60% among neutropenic patients ($P = .007$). Primary antifungal prophylaxis consisting of only fluconazole was administered to allogeneic hematopoietic stem cell transplant recipients and patients with acute leukemia, so the difference in mortality rates cannot be explained in terms of this treatment. One probable reason for such a discrepancy is that nonneutropenic patients were less closely monitored for IA, leading to suboptimal management and late antifungal therapy. We confirm that nonneutropenic patients are less symptomatic than neutropenic patients; notably, there were fewer cases of fever among nonneutropenic patients [13, 20], as well as fewer cases of cough and chest pain. One-half of the fatalities among patients who received continuous corticosteroid therapy occurred within 5 days after IA diagnosis. A similarly high mortality rate has already been reported for patients with mild immunosuppression and even for patients with liver cirrhosis [20, 31, 32].

Mycological examination was performed for 90% of our patients. Routine microscopic examination of BAL fluid samples combined with BAL culture, had a sensitivity of 69% in this study, which is higher than generally reported. However, numbering IA only from the laboratory listing of *Aspergillus* isolates may be insufficient to draw the features of IA in the whole of an institution [33]. Intercurrent bacterial, cytomegalovirus, and *P. jiroveci* pneumonia were frequent, particularly among nonneutropenic patients, underlining that the presence of *Aspergillus* in respiratory samples (in addition to another infectious agent) should not be systematically considered to represent simple colonization [34]. Among the 46 patients (52%) who underwent prospective *Aspergillus* GM antigenemia testing after 2000, 34 (74%) underwent regular monitoring. The sensitivity of the *Aspergillus* GM antigenemia test was 65% overall, and it was 88% for patients with proven or probable IA; no difference was observed between neutropenic and nonneutropenic patients. The contribution of CT to early diagnosis of IA is now well recognized [9, 11]. However, early CT disrupts the protective environment during the period of aplasia. The sensitivity of the halo sign was low in neutropenic patients; this sign was never present in our nonneutropenic patients, but it has recently been shown that the lack of the halo sign has no negative predictive value [20].

In conclusion, IA remains a major life-threatening infection among patients with prolonged neutropenia, although protective measures (such as air filtration) significantly reduced its incidence. This 6-year survey at a whole institution, using international criteria, underlines the high number of proven and

Table 3. Comparison of clinical and biological features between neutropenic and nonneutropenic patients with invasive aspergillosis (IA).

Characteristic	Neutropenic patients (n = 52)	Nonneutropenic patients (n = 36)	All patients (n = 88)	P
Ratio of male to female patients	1.74:1	1.4:1	1.6:	.63
Age, mean years	46	61	52	.001[a]
Case classification				
Proven IA	8 (15)	4 (11)	12 (14)	
Probable IA	31 (60)	21 (58)	52 (59)	.77
Possible IA	13 (25)	11 (31)	24 (27)	
Clinical sign				
Fever	50 (96)	25 (69)	75 (85)	.0005[a]
Dyspnea	31 (60)	26 (72)	57 (65)	.22
Cough	35 (67)	10 (28)	45 (51)	.0003[a]
Chest pain	17 (33)	4 (11)	21 (24)	.02[a]
Hemoptysis	3 (6)	3 (8)	6 (7)	.69
Intercurrent bacterial pneumonia	8 (15)	20 (56)	28 (33)	.0007[a]
Associated opportunistic infection[b]	3 (6)	6 (17)	9 (10)	.15
Outcome				
Death	31 (60)	32 (89)	63 (71.5)	
Recovery	16 (31)	3 (8)	19 (21.5)	.007[a]
Unknown	5 (9)	1 (3)	6 (7)	
Sensitivity of test, *n/N* (%)				
BAL fluid examination[c]	24/41 (58)	22/26 (85)	46/67 (69)	.025[a]
Aspergillus GM antigenemia test	7/11 (64)	15/23 (65)	22/34 (65)	1
Antibody serologic test	1/16 (6.25)	10/21 (48)	11/37 (30)	.01[a]
Thoracic CT sign, *n/N* (%)				
Segmental areas of consolidation	26/42 (62)	9/24 (37.5)	35/66 (53)	.056
Nodules	18/42 (43)	11/24 (46)	29/66 (44)	.81
Cavitated nodules	8/42 (19)	6/24 (25)	14/66 (21)	.57
Ground-glass attenuation	15/42 (36)	5/24 (21)	20/66 (30)	.21
Pleural effusion	16/42 (38)	8/24 (33)	24/66 (36)	.7
Halo sign	4/42 (9.5)	0/24 (0)	4/66 (6)	.29
Air crescent sign	1/42 (2.5)	0/24 (0)	1/66 (1.5)	1
Bell sign	3/42 (7)	1/24 (4)	4/66 (6)	1
Aspergillosis cavity	6/42 (14)	2/24 (8)	8/66 (12)	.7

NOTE. Data are no. (%) of patients, unless otherwise indicated. BAL, bronchoalveolar lavage; GM, galactomannan.

[a] $P < .05$ for a comparison of neutropenic and nonneutropenic patients.

[b] Intercurrent *Pneumocystis jiroveci* or cytomegalovirus infection.

[c] Positive results of a direct examination and/or culture of a BAL fluid specimen.

probable cases in nonneutropenic patients. Management guidelines are needed for such patients, who have a higher mortality rate than their neutropenic peers. Clinical signs are frequently lacking in mildly immunosuppressed patients, but the diagnostic value of biological tests, such as mycological examination of BAL fluid specimens and *Aspergillus* GM assay, is at least as good as that for neutropenic patients. A wide range of risk factors must be taken into account, including continuous corticosteroid therapy (even at low doses) and *Aspergillus* colonization of the respiratory tract. Finally, measures are required to avoid or reduce respiratory tract colonization in patients with chronic pulmonary diseases.

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