Invasive aspergillosis in patients with hematologic malignancies: incidence and description of 127 cases enrolled in a single institution prospective survey from 2004 to 2009

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ABSTRACT

Background
The study objectives were: 1) to report on invasive aspergillosis patients in a hematology department; and 2) to estimate its incidence according to the hematologic diagnosis.

Design and Methods
A prospective survey of invasive aspergillosis cases was undertaken between January 2004 and December 2009 in the hematology department of a university hospital. Meetings with clinicians, mycologists and infection control practitioners were organized monthly to confirm suspected aspergillosis cases. Demographic characteristics, clinical and complementary examination results were recorded prospectively. Information on hospitalization was extracted from administrative databases. Invasive aspergillosis diagnosis followed the European Organization for Research and Treatment of Cancer criteria, and proven and probable IA cases were retained. A descriptive analysis was conducted with temporal trends of invasive aspergillosis incidence assessed by adjusted Poisson regression.

Results
Overall, 4,073 hospitalized patients (78,360 patient-days) were included in the study. In total, 127 (3.1%) patients presented invasive aspergillosis. The overall incidence was 1.6 per 1,000 patient-days (95% confidence interval: 1.4, 1.9) with a decrease of 16% per year (-1%, -28%). The incidence was 1.9 per 1,000 patient-days (1.5, 2.3) in acute myeloid leukemia patients with a decrease of 20% per year (-6%, -36%). Serum *Aspergillus* antigen was detected in 89 (71%) patients; 29 (23%) had positive cultures, and 118 (93%), abnormal lung CT scans. One-month mortality was 13%; 3-month mortality was 42%. Mortality tended to decrease between 2004 and 2009.

Conclusions
Invasive aspergillosis incidence and mortality declined between 2004 and 2009. Knowledge of invasive aspergillosis characteristics and its clinical course should help to improve the management of these patients with severe disease.

Key words: invasive aspergillosis, surveillance, hematologic disease, incidence, hospital.

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Introduction

Invasive aspergillosis (IA) is a major concern in hematology departments because of its high incidence and associated mortality.[1-3] The mortality rate usually exceeds 50% and can reach 90% in allogeneic hematopoietic stem cell transplantations recipients.[1,4,5] IA occurs mainly in immunosuppressed patients with prolonged neutropenia induced by chemotherapy and/or patients who undergo hematopoietic stem cell transplantation.[4,6-8] IA prevention and treatment remain important issues. Recently-observed improvement in survival[9] has been related to changes in clinical practices, and despite greater risk of aplasia, the prognosis of hematologic diseases has improved in recent years with more efficient chemotherapies.[10]

IA incidence varies according to underlying hematologic disease and studies reported, being between 5% and 24% in acute leukemia patients[11-14] and between 3% and 11% in allogeneic stem cell transplantation.[15-17] Medical prophylaxis with posaconazole[18-19] and/or prevention strategies taking environmental factors into account[20-21] could have contributed to a decrease in IA incidence. However, to the best of our knowledge, this IA incidence trend has not yet been described. On the other hand, hospital infection surveillance has been shown to be efficient in reducing infection rates.[22] Detailed reports on IA patient series are helpful in improving knowledge of the disease and potential changes in its natural history. Also, monitoring of recent trends and the clinical course of IA in hematology patients are useful in evaluating current global medical support,[23] which may lead to the establishment of best-care strategies for patients at high risk of IA.

The objectives of this prospective survey-study were: 1) to estimate the incidence of IA according to underlying diagnosis; and 2) to describe the clinical and paraclinical characteristics of patients with IA in a hospital hematology department between 2004 and 2009.

Design and Methods

Setting

Edouard Herriot Hospital is a 1,000-bed tertiary care institution composed of 32 blocks. One of these blocks accommodates the hematology department (42 beds), which is divided into 3 intensive care units. Two of these units contain 14 single rooms each, of which 8 rooms are equipped with laminar airflow (LAF), and 6 have no specific air treatment. The third unit was made up of 10 conventional rooms, 4 with LAF until October 1, 2005, when it was relocated to an adjoining modular unit containing 14 rooms equipped with positive pressure isolation and HEPA filtration.

Study design and data sources

A prospective survey of IA cases was undertaken from January 1, 2004. A detailed description of this surveillance can be found elsewhere.[21] For the present study, the data were censored at December 31, 2009. Multiple sources allowed us to identify suspected IA with the highest sensitivity. Suspected IA cases were declared by hematologists, detected by prospective surveillance of healthcare-associated infections in the department, or found by the mycology department. Multidisciplinary meetings with at least one clinician, one mycologist and one infection control practitioner were organized every month to confirm suspected IA cases, all of which were categorized as possible, probable or proven, according to standardized definitions of the European Organization for Research and Treatment of Cancer (EORTC).[24] Demographic characteristics, risk factors, clinical and mycological features, as well as CT scan reports, were recorded prospectively for each patient on a standardized form. Patients were followed for at least three months after IA diagnosis.

Hospital stays in the hematology department were extracted exhaustively for the period 2004-2009 from the French equivalent of the Diagnosis-Related Group program (Programme de Médicalisation des Systèmes d'Information, PMSI). The PMSI database was completed by the physician in charge of each patient and included standard discharge summaries containing compulsory patient information (gender, age, origin of admission) and diagnoses of underlying diseases according to codes from the 10th revision of the International Classification of Diseases. Other available information concerned dates of hospital or hematology department admission and discharge with corresponding length of stay, as well as in-hospital mortality (French Technical Hospitalization Information Agency website *http://www.atih.sante.fr/en/index.php*. Accessed May 14, 2009).

Patients

All patients hospitalized in these hematology units were included in the survey. IA diagnosis in immunocompromised patients was based on an international consensus from experts of the EORTC and the National Institute of Allergy and Infectious Diseases Mycoses Study Group.[24] This group defined 3 levels of diagnosis: proven, probable, or possible. The analysis was restricted to proven and probable cases. Proven IA was defined as: histopathological data, positive culture of previously sterile sites, and clinical features compatible with IA. Probable IA was defined by one host factor criterion, one microbiological criterion and one major clinical criterion (or 2 minor criteria).[24] Bone transplant recipients were not formally excluded because the focus was not on the underlying disease, i.e. acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL).

Statistical analysis

Quantitative variables were described as number and percentage, and qualitative variables as median and interquartile range (IQR). IA incidence was calculated for 1,000 patient-days of hospitalization with 95% confidence interval (95% CI). To study temporal trends of IA incidence, Poisson regression was fitted with number of IA as the dependent variable, years of diagnosis as the independent variables and the number of patient-days at risk as an offset. All statistical tests were two-tailed and $P<0.05$ was considered statistically significant. All data were analyzed anonymously with Stata 8.0 software (Stata Corp.). Our study received no external funding. According to French law, current surveillance of nosocomial infections in hospital and epidemiological observational surveys without any intervention do not need institutional review board authorization or written consent.

Results

Participants

Overall, 4,073 hospitalized patients accounting for 78,360 patient-days at risk were included. The male/female sex ratio was 1.24 and median age was 51 years (IQR: 35.1-60.7 years). In total, 2,078 (51%) patients were hospitalized for acute myeloid leukemia (AML) and 850 (21.9%) for acute lymphoid leukemia (ALL). One hundred and twenty-seven (3.1%) patients had IA. Among patients with IA, 91 had AML and 19 had ALL; the IA incidence rates were 4.4% and 2.2%, respectively.

Invasive aspergillosis incidence

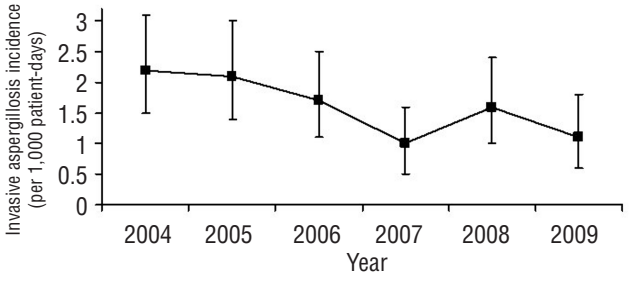
Overall incidence was 1.6 per 1,000 patient-days (95% CI: 1.4, 1.9) (Table 1, Figure 1). IA incidence was 1.9 *per* 1,000 patient-days (95% CI: 1.5, 2.3) among AML patients and 1.3 *per* 1,000 patient-days (95% CI: 0.8, 2.0) among ALL patients. Univariate Poisson regression showed that IA incidence declined during the study period (-16% *per* year; 95% CI: -1%, -28%, *P*=0.006). IA incidence decreased among AML patients (-20% year; 95% CI: -6%, -36%, *P*=0.005), whereas it did not change among patients with ALL (-19% *per* year; 95% CI: -5%, +9%, *P*=0.19) or other hematologic diseases (+7% *per* year; 95% CI: -23%, +41%, *P*=0.64). Multivariate Poisson regression, adjusted for sex and age, gave similar results (*data not reported*).

Invasive aspergillosis patients

Table 2 details the IA patient characteristics and clinical features. The male/female sex ratio was 1.2, and median age was 56 years (IQR: 43.1-63.6 years). Tests for serum *Aspergillus* antigen (Platelia Galactomannan, Bio-Rad®; cut-off value of ≥0.5) were performed in 125 (98%) patients with detection in 89 (71%) of them. Chest CT scans were taken in 122 (97%) patients and 118 (97%) of them were abnormal. A halo sign was found in 96 (81%) of those patients with positive chest CT scans. Pulmonary IA was diagnosed in 109 (86%) patients; 6 (5%) had sinusitis IA, and 12 (9%) disseminated IA. Overall, 110 (87%) patients had probable IA, and 17 (13%) had proven IA. Among the 17 patients with proven IA, the diagnosis was made in 11 after positive biopsy, in 4 after needle aspiration, and in 2 after both biopsy and aspiration. Among patients with proven IA, 8 had pulmonary IA, 3 had sinusitis IA, and 6 had disseminated IA.

Hospital course

Table 3 reports the time to diagnosis and the clinical course of IA. The median delay between admission and IA diagnosis was 20 days (minimum 0, maximum 185 days), and the median delay between aplasia onset and IA diagnosis was 14 days; minimum -15 (i.e. 15 days before admission), maximum 198 days. IA was diagnosed in 14 (11%) patients on the day of admission; among them, one patient had previous allogeneic transplant and 4 patients had previous RIC-allogeneic transplant within six months before IA. In total, 8 patients were directly admitted from home for care of suspected IA (diagnosis of IA the day of hospital admission) while 6 came from other in-hospital units. IA was diagnosed in 7 (6%) patients during the first



The incidence is the number of invasive aspergillosis cases per 1,000 patient-days at risk; 95% are shown. Vertical lines represent 95% confidence interval. IA incidence declined during the study period (Poisson regression, -16% per year; 95% CI: -1%, -28%, P=0.006).

Figure 1. Incidence rate of invasive aspergillosis per 1,000 patient-days, Hematology Department, Edouard Herriot Hospital, 2004-2009.

Table 1. Annual incidence of proven and probable invasive aspergillosis, Hematology Department, Edouard Herriot Hospital, 2004-2009.

Characteristics	Year 2004	2005	2006	2007	2008	2009	Overall
Population							
Number of patients	674	713	694	623	658	711	4,073
Cumulative patient-days at risk	13,875	13,108	12,677	13,177	12,834	12,689	78,360
Number of patients with AML	356	364	339	345	334	340	2,078
Cumulative patient-days at risk	8,766	8,150	7,997	8,786	8,194	7,131	49,024
Number of patients with ALL	134	166	117	89	138	206	850
Cumulative patient-days at risk	2,188	2,343	2,169	1,938	2,612	3,251	14,501
Number of patients with other hematologic disease	184	183	238	189	186	165	1,145
Cumulative patient-days at risk	2,921	2,615	2,511	2,453	2,028	2,307	14,835
Number of IA (%)							
Overall population	31 (4.6)[1]	28 (3.9)	21 (3.0)	13 (2.1)	20 (3.0)	14 (2.0)	127 (3.1)
AML patients	23 (6.5)	23 (6.3)	14 (4.1)	9 (2.6)	13 (3.9)	9 (2.7)	91 (4.4)
ALL patients	5 (3.7)	4 (2.4)	2 (1.7)	2 (2.3)	3 (2.2)	3 (1.5)	19 (2.2)
Other patients	3 (1.6)	1 (0.6)	5 (2.1)	2 (1.1)	4 (2.2)	2 (1.2)	17 (1.5)
IA incidence rate[2] (95% CI)							
Overall population	2.2 (1.5, 3.1)	2.1 (1.4, 3.0)	1.7 (1.1, 2.5)	1.0 (0.5, 1.6)	1.6 (1.0, 2.4)	1.1 (0.6, 1.8)	1.6 (1.4, 1.9)
AML patients	2.6 (1.7, 3.9)	2.8 (1.8, 4.2)	1.8 (1.0, 2.7)	1.0 (0.5, 1.9)	1.6 (0.9, 2.6)	1.3 (0.6, 2.3)	1.9 (1.5, 2.3)
ALL patients	2.3 (0.8, 5.1)	1.7 (0.5, 4.1)	0.9 (0.2, 3.0)	1.0 (0.2, 3.4)	1.1 (0.3, 3.1)	0.9 (0.2, 2.5)	1.3 (0.8, 2.0)
Other patients	1.0 (0.3, 2.8)	0.4 (0.2, 1.9)	2.0 (0.7, 4.4)	0.8 (0.1, 2.7)	2.0 (0.6, 4.8)	0.9 (0.1, 2.9)	1.1 (0.7, 1.8)

IA: invasive aspergillosis; AML: acute myeloid leukemia; ALL: acute lymphoid leukemia; CI: confidence interval. [1]Data are numbers (%), i.e. "31 (4.6)" means 31 patients with IA per 674 hospitalized patients, the proportion of patients who had IA in the population was 4.6%. [2]Number of newly-diagnosed IA per 1,000 patient-days at risk.

Table 2. Characteristics and clinical features of patients with invasive aspergillosis diagnosis, Hematology Department, Edouard Herriot Hospital, 2004-2009.

Characteristics	Value (n=127)
At admission	
Gender, female	57/126 (45)
Age, median (IQR)	55.6 (43.1-63.6)
Year of admission	
2004-2005	58/127 (46)
2006-2007	36/127 (28)
2008-2009	33/127 (26)
Patient origin	
Home	92/126 (73)
Other hospital service	5/126 (4)
Other hospital	29/126 (23)
Hematologic disease	
Acute myeloid leukemia	97/127 (76)
Acute lymphoid leukemia	17/127 (14)
Non-Hodgkin's lymphoma	2/127 (2)
Chronic myeloid leukemia	0/127 (0)
Chronic lymphocytic leukemia	3/127 (2)
Myeloma	3/127 (2)
Other[1]	5/127 (4)
Disease course	
Induction chemotherapy	60/127 (47)
Reinduction chemotherapy	4/127 (3)
Consolidation chemotherapy	8/127 (7)
Relapse	27/127 (21)
Progression	8/127 (6)
Other	20/127 (16)
Previous stem cell transplant within 6 months	
None	104/127 (82)
Autologous transplant	3/127 (2)
Allogeneic transplant	11/127 (9)
RIC-allogeneic transplant	9/127 (7)
During hospital stay in the department	
Aplasia[1]	109/127 (86)
Corticoid use	31/126 (25)
Room with controlled ventilation[2]	72/127 (57)
Stay in intensive care unit	23/127 (18)
Death within 1 month	17/127 (13)
Death within 3 months	53/127 (42)
Clinical signs or symptoms at diagnosis suspicion	
Respiratory (cough, dyspnea)	100/126 (79)
Cutaneous	3/126 (2)
Neurological	8/126 (2)
Sinusitis	7/126 (6)
Fever >38°C[3]	122/126 (97)
Lung CT scan performed	122/127 (96)
Abnormal	118/122 (97)
CT scan finding	
Halo sign	96/118 (81)
Excavation	4/118 (4)
Nodules without halo sign	10/118 (8)
Other findings	8/118 (7)
Serum *Aspergillus* antigen test performed[4]	125/127 (98)
Positive serum *Aspergillus* antigen test	89/125 (71)
Mycological samples taken	100/126 (79)
Positive mycological samples[5]	46/100 (46)
EORTC diagnosis	
Proven	17/127 (13)
Probable	110/127 (87)
Invasive aspergillosis localization	
Pulmonary	109/127 (86)
Sinusitis	6/127 (5)
Disseminated[6]	12/127 (9)

Data are numbers/number known (%) or specified otherwise. [1]Less than 500 neutrophils/mm³ for >10 days. [2]Laminar air flow or positive pressure isolation, and high efficiency particulate filtration. [3]Persistent fever for >96 h refractory to appropriate antibiotic treatment. [4]≥2 positive serum antigens against Aspergillus *species. [5]Positive filamentous fungi and/or culture and/or* Aspergillus *antigen. [6]Localizations are: cerebral and pulmonary (n=7); sinusitis and pulmonary (n=2); digestive and pulmonary (n=1); cutaneous and pulmonary (n=1); sinusitis, cerebral, cutaneous and pulmonary (n=1).*

ten days of hospital stay. Among the 78 patients with positive circulating *Aspergillus* antigen and abnormal CT scans, 12 (15%) had 2 positive examinations on the same day and 42 (54%) were positive for circulating *Aspergillus* antigen before the detection of a pathological image on CT scan. For these last 42 patients, the median time interval between positive antigen and positive CT scan was five days (IQR: 2, 7 days). In 24 (31%) patients, CT scan detected a pathological image before a positive circulating *Aspergillus* antigen result with a median delay of three days (IQR: 1.5, 7.5 days). Figure 2 shows the relationship between the number of patients with aplasia and IA occurrence according to time period. It suggests an increase in IA incidence with aplasia.

Mycological samples

A total of 127 samples were analyzed among 100 patients screened for mycological evidence. Thirty-three (26%) samples were positive for filamentous fungi on direct examination, 32 (25%) for culture, and 26 (20%) for *Aspergillus* antigen. Overall, 70 (55%) samples were positive for at least microscopy and/or culture and/or *Aspergillus* antigen (Pastorex aspergillus). Of 82 bronchoalveolar lavages, 12 (15%) were positive for filamentous fungi on direct examination, 17 (21%) for culture, and 16 (20%) for *Aspergillus* antigen. Totally, 54 (66%) bronchoalveolar lavages were positive for at least microscopy and/or culture and/or *Aspergillus* antigen. In total, 29 patients had at least one positive culture for *Aspergillus spp.*, 16 (55%) were positive for *A. fumigatus*, 5 (17%) for *A. flavus*, 3 (10%) for *A. niger*, 2 (6%) for *A. terreus*, one (4%) for *A. nidulans*, and one (4%) for *A. sp*. One patient was co-infected by *A. fumigatus* and *A. flavus*.

Invasive aspergillosis mortality

All-cause mortality was 13% (n=17) at one month and 42% (n=53) at three months after IA. All-cause mortality were respectively 14% (n=14) and 6% (n=1) among AML and ALL patients at one month, 38% (n=37) and 53% (n=9) at three months after IA. Figure 3 reports one-month and 3-month all-cause mortality in IA patients by time periods. Between 2004 and 2009, no statistically significant trend towards a decrease was observed in one-month (P=0.20) and 3-month (P=0.59) all-cause mortality. The main causes of death before Day 30 after IA were: IA (n=7), hematologic disease (n=1), IA and hematologic disease (n=5), other or unknown (n=4). The main causes of

death before Day 90 after IA were: IA (n=11), hematologic disease (n=6), IA and hematologic disease (n=21), other or unknown (n=15).

Discussion

The objectives of the study were to report the incidence and clinical features of IA among hospitalized hematology patients. Knowledge of the clinical presentation of diseases is an important tool for sound clinical management.[23] Here, we detailed the clinical description of patients with IA in a hematology unit, based on a prospective survey system. IA incidence was 1.6 *per* 1,000 patient-days (95% CI: 1.4, 1.9), with a slightly linear decrease (16% *per* year) observed during the 2004-2009 study period.

Table 3. Diagnosis and clinical course of invasive aspergillosis, Hematology Department, Edouard Herriot Hospital, 2004-2009.

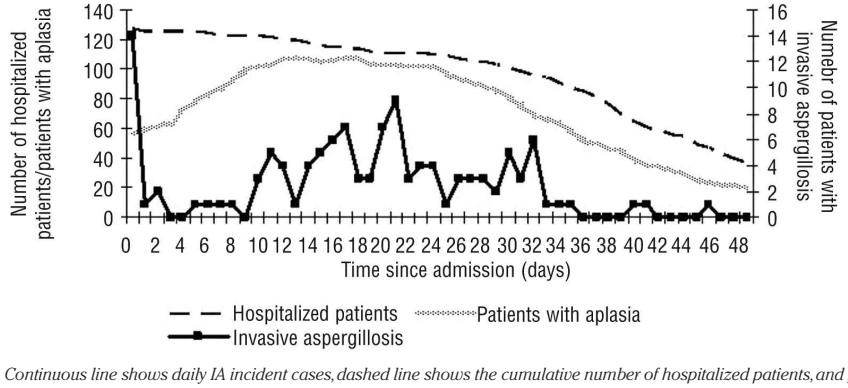
Characteristics, days, median (IQR)[1]	Acute myeloid leukemia (n=91)	Acute lymphoid leukemia (n=19)	Other hematologic disease (n=17)	Overall (n=127)
General				
Length of stay in the department	41 (34, 50)	45 (34, 52)	36 (16, 47)	41 (33, 51)
Length of aplasia	29 (23, 37.5)	25 (18, 40)	22 (8, 35)	28 (22, 37)
Delay between hospitalization and aplasia	4 (0, 9)	6.5 (0, 9)	0 (0, 12)	8 (5, 12)
Delay between hospitalization and IA diagnosis	20 (13, 27)	19 (15, 31.5)	12 (7, 21)	20 (12, 27)
Delay between aplasia and IA diagnosis	14 (10, 21)	13 (7, 15)	10 (0, 21)	14 (9, 21)
IA diagnosis				
Delay between clinical suspicion of IA and first positive serum *Aspergillus* antigen test	0 (-2, 2)	1 (0, 4.5)	1 (-4, 9)	0 (-1, -2)
Delay between clinical suspicion of IA and positive pulmonary CT Scan	1 (0, 2)	1 (0, 3.5)	1 (0, 2)	1 (0, 2)

IQR: interquartile range; IA: invasive aspergillosis.

To our knowledge, data on the IA incidence rate in hospitalized hematology patients are limited while cumulative incidence (i.e. attack rate) has been reported extensively in patients with various hematologic diseases.[3,4,7,14,25-27] While IA increased in the 1980s-1990s in the general population,[2] no reduction in IA incidence has been observed in hematology patients.[3,28] In our study, the decrease in IA incidence could be explained by medical prophylaxis with posaconazole which has been used systematically in all patients with AML in induction chemotherapy since 2007 in our setting.[18,29] The study of Cornely and colleagues[18] reported an IA event rate in the posaconazole group of approximately 1%, whereas the event rate that we observed from 2008-2009 was 3.3% in patients with AML. The observed attack rate of IA in AML patients for 2004-2007 and 2008-2009 was 4.9% and 3.3% (P=0.04), respectively. Also the absolute differences were 6.0% in the RCT[18] *versus* 1.6% in the present observational context. This shows the differences in intervention according to the study design: RCT *versus* observational data. Calibration of the trial, inclusion criteria, and standardization of measurements are cornerstone of RCT for increasing internal validity. In a less favorable context, such as observational design, we can expect prophylaxis to have less effect.[30] However, the difference was significant between the two periods. It agrees with the study of Cornely and colleagues and reinforces its conclusion.[18]

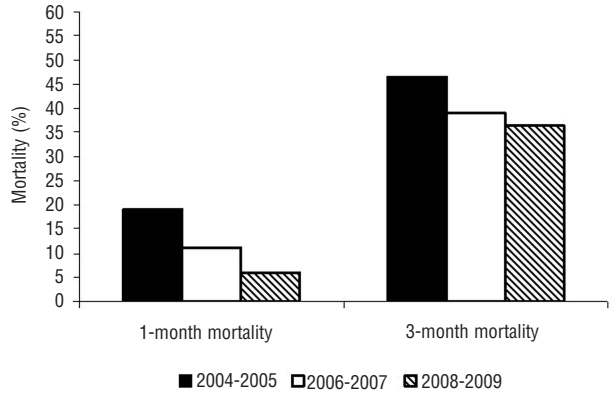
Another explanation could be better control of environmental exposure (i.e. specially ventilated rooms) in the department.[21] Moreover, the decrease of IA incidence was most probably not due to a lower incidence of *Aspergillus* antigen or a reduced number of positive CT scans. Indeed, *Aspergillus* antigen was usually investigated in patients two times a week according to a local protocol. CT scans were performed after clinical suspicion and no major practice change was reported.

The first signs suggesting IA appeared in 106 (84%) patients more than ten days post-admission in the department. A cut off of seven days has often been recognized as an incubation period for fungal infections.[8] However, the incubation period preceding IA is still not known. According to our data, it can be argued that, in severely immunocompromised hosts with depletion of pulmonary conidia clearance, the incubation period ranges from ten to 35 days. Thus, IA diagnosed before ten days of hospitalization might be of undetermined origin, but could be related to early hospital exposure in severely immuno-



Continuous line shows daily IA incident cases, dashed line shows the cumulative number of hospitalized patients, and gray line shows the cumulative number of patients with aplasia. Data were censored at Day 50 after admission in the unit.

Figure 2. Description of cumulative numbers of hospital stays, aplasia and invasive aspergillosis over time since the day of admission in the unit for patients with IA, Hematology Department, Edouard Herriot Hospital, 2004-2009.



No statistically significant trend towards a decrease was observed in one-month (P=0.20) and 3-month (P=0.59) all-cause mortality.

Figure 3. One-month and 3-month all-cause mortality in patients with invasive aspergillosis by time periods (2004-2005, 2006-2007, 2008-2009), Hematology Department, Edouard Herriot Hospital, 2004-2009.

compromised patients. Another explanation might be that patients are colonized by *Aspergillus* and that chemotherapy or stem cell transplant facilitates invasive infection. Indeed, 5 patients had previous allogeneic transplant; these cases of IA can be related to the second peak of IA which is usually observed in transplant recipients. Finally, if the time period for IA occurrence is ten days or more, infection is probably hospital-acquired. It is clear from Figure 2 that the shape of IA case distribution differed after ten days, indicating that different determinants could explain these two patterns of IA incidences.

We noted that the 3-month all-cause mortality of 42% was much lower than in another study (64%).[31] It has been reported that 3-month mortality decreased from 45% in 1990-2001 to 22% in 2002-2004.[9] Moreover, Pagano *et al.* reported a 120-day overall mortality of 33% in AML patients with IA while the 3-month mortality was 38% in our cohort.[28] We observed a similar trend in a more recent period, which could be related to earlier diagnosis, more active antifungal drugs, and/or changes in hematology practices. It has been suggested that late IA diagnosis could lead to poor prognosis.[32] In our study, continuous effort was made by the medical staff to diagnose IA as early as possible. Indeed, serum *Aspergillus* antigen was tested two times/week during patient aplasia. Furthermore, lung CT scans were taken 24 h or less after clinical suspicion in most cases, reflecting the close attention paid by clinicians and radiologists to invasive fungal infections. Indeed, most lung CT scans revealed the halo sign, which is usually seen early after onset. Our CT scan findings were then comparable to those of Greene *et al.*[33] The incidence of halo signs and nodules without sign were 81% and 8%, respectively, in our series. Greene reported incidences of 60.9% and 33.6%, respectively, in a broad sample of patients with IA. Our study cannot distinguish between the effects of improved chemotherapy or IA management on survival. However, it should be noted that acute leukemia patients, and ideally patients with other hematologic malignancies, should be closely evaluated and monitored to control the risk of IA. High clinical suspicion that leads to early diagnosis might be considered by clinicians.

These results are encouraging and supported by some study strengths. Data were collected prospectively, on a standardized form, with multidisciplinary validation of IA cases by experts. Cases conformed to standardized international definitions.[24] The incidence trend was assessed in the entire patient cohort hospitalized during the study period, showing the actual IA incidence in hematology patients and adjusted for age and gender. However, some limitations must be mentioned. First, medical prophylaxis with posaconazole was not recorded in our surveillance system as this treatment was introduced for AML patients in induction chemotherapy during the year 2007. Second, external validity may be limited because the study was performed in a single institution. However, this weakness could be counterbalanced by the fact that the study included all patients of a typical hematology unit and no major changes occurred in diagnostic methods. Third, the study may have been underpowered, failing to show significant decreasing trends in IA mortality. In addition, limited data were available to adjust incidence trends with confounding factors such as aplasia, because this information was collected only for IA cases.

In summary, IA remains a frequent and highly lethal opportunistic infection in hematology patients despite a decrease in its incidence and probable mortality. Precise assessment of patients' characteristics, clinical signs, and diagnostic tests, as well as knowledge of IA clinical course, would improve the management of these patients at high risk of infection.

Authorship and Disclosures

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