Epidemiological trends in invasive aspergillosis in France: the SAIF network (2005–2007)

O. Lortholary[1,2,3], J.-P. Gangneux[4,5], K. Sitbon[1,2], B. Lebeau[6], F. de Monbrison[7], Y. Le Strat[8], B. Coignard[8], F. Dromer[1,2] and S. Bretagne[1,9,10], for the French Mycosis Study Group*

1) *Institut Pasteur, Centre National de Référence Mycologie et Antifongiques, Unité de Mycologie Moléculaire, Paris,* 2) *CNRS URA3012, Paris,* 3) *Université Paris-Descartes, Hôpital Necker-Enfants Malades, Service des Maladies Infectieuses et Tropicales, Centre d'Infectiologie Necker-Pasteur, Paris,* 4) *Laboratoire de Parasitologie-Mycologie, Centre Hospitalo-Universitaire de Rennes,* 5) *EA SeRAIC 4427, IFR 140, Université Rennes 1, Rennes,* 6) *Laboratoire de Parasitologie-Mycologie, CHU de Grenoble, Grenoble,* 7) *Laboratoire de Parasitologie-Mycologie, Centre Hospitalo-Universitaire de Lyon, Lyon,* 8) *Infectious Diseases Department, Institut de Veille Sanitaire, Saint Maurice,* 9) *Laboratoire de Parasitologie-Mycologie, Hôpital Henri Mondor-APHP, Créteil and* 10) *UMR BIPAR Ecopham, Université Paris Est Créteil, Créteil, France*

Abstract

A prospective (2005–2007) hospital-based multicentre surveillance of EORTC/MSG-proven or probable invasive aspergillosis (IA) cases whatever the underlying diseases was implemented in 12 French academic hospitals. Admissions per hospital and transplantation procedures were obtained. Cox regression models were used to determine risk factors associated with the 12-week overall mortality. With 424 case-patients included, the median incidence/hospital was $0.271/10^3$ admissions (range 0.072–0.910) without significant alteration of incidence and seasonality over time. Among the 393 adults (62% men, 56 years (16–84 years)), 15% had proven IA, 78% haematological conditions, and 92.9% had lung involvement. Acute leukaemia (34.6%) and allogeneic stem cell transplantation (21.4%) were major host factors, together with chronic lymphoproliferative disorders (21.6%), which emerged as a new high-risk group. The other risk host factors consisted of solid organ transplantation (8.7%), solid tumours (4.3%), systemic inflammatory diseases (4.6%) and chronic respiratory diseases (2.3%). Serum galactomannan tests were more often positive (≥69%) for acute leukaemia and allogeneic stem cell transplantation than for the others (<42%; $p < 10^{-3}$). When positive (n = 245), cultures mainly yielded *Aspergillus fumigatus* (79.7%). First-line antifungal therapy consisted of voriconazole, caspofungin, lipid formulations of amphotericin, or any combination therapy (52%, 14%, 8% and 19.9%, respectively). Twelve-week overall mortality was 44.8% (95% CI, 39.8–50.0); it was 41% when first-line therapy included voriconazole and 60% otherwise (p <0.001). Independent factors for 12-week mortality were older age, positivity for both culture and galactomannan and central nervous system or pleural involvement, while any strategy containing voriconazole was protective.

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Corresponding author: S. Bretagne, Institut Pasteur, Centre National de Référence Mycologie et Antifongiques, Unité de Mycologie Moléculaire, 25, rue du Dr Roux, 75015 Paris, France
E-mail: bretagne@univ-paris12.fr

*Members of the Surveillance des Aspergilloses Invasives en France (SAIF) study group are listed in the Appendix section.

Introduction

Invasive aspergillosis (IA) remains the main cause of morbidity and mortality in patients undergoing allogeneic haematological stem cell transplantation (HSCT), but characteristics of these patients and those with myeloma [1], solid tumours [2] and solid-organ transplant (SOT) [3,4], and management of their diseases, are changing [5]. Additionally, increased numbers of cases due to underlying bronchial damage [6] and/or associated with intensive care [7,8], and fewer cases related to advanced stages of HIV infection, are now reported [9]. Therefore, the profile of patients considered at risk of IA continues to expand while the outcome seems to improve.

Trying to describe the epidemiology of IA is challenging as the diagnosis requires standardized criteria [10,11]. To overcome the limitations of setting specific [12] or single hospital

[2] studies, we implemented a dedicated network to prospectively collect all cases of IA. Our aim was to describe its incidence per hospital whatever the underlying diseases, its potential variations according to centres and transplant procedures, and to assess the contribution of diagnostic tools, the first-line antifungals used and the prognostic factors.

Patients and Methods

Data collection

A prospective surveillance programme (SAIF for 'Surveillance des Aspergilloses Invasives en France') was implemented in three regions (Paris-Ile de France, Grand Ouest and Rhône-Alpes) by the National Reference Centre for Mycoses and Antifungals (NRCMA, Institut Pasteur) with the participation of 12 acute care teaching hospitals and the French National Public Health Surveillance Institute (Institut de Veille Sanitaire). All new IA episodes were recorded whatever the age and the underlying disease by each local microbiologist, which limited the risk of missing cases because at least one microbiological criterion was compulsory for validation [10]. Each case was notified through a secured website using a standardized questionnaire and analysed by a local committee. To maintain adhesion to the network, the coordination committee organized semestrial meetings with participating microbiologists. Demographics, underlying conditions, diagnostic tools, dates of hospitalization, first-line antifungal therapy and outcome at day 90 were recorded. The study was approved by the Institut Pasteur Institutional Review Board.

The diagnostic investigations and therapeutic management followed local practices. Only proven and probable IA according to 2002 European Organization for Research and Treatment of Cancer and Mycoses Study Group criteria were considered [10]. The date of the first radiological or microbiological criteria was considered as the date of IA diagnosis. Dissemination was defined as more than two non-contiguous organs involved. The threshold of positivity for the galactomannan (GM) index (Platelia Aspergillus; Biorad, Marnes-la-Coquette, France) in serum was 1 for 2005 according to the manufacturer's recommendations at that time, and 0.5 thereafter. Missing information and ambiguous answers were checked by the database manager with the corresponding microbiologist and each case was validated by three of us.

As invasive aspergillosis was managed in the referral centre where the patient was followed for his immunosuppressive condition, at least in the case of haematological malignancy or transplant procedure, we decided to use patient admissions per hospital as well as numbers of HSCT and SOT recipients in participating hospitals as denominators obtained through national health statistics http://www.platines.sante.gouv.fr/.

Statistical analysis

Means and standard deviations (SDs) are shown when distributions were confirmed normal while median and IQR are used otherwise. We compared baseline characteristics of groups by use of the χ^2 test or Fisher's exact test for categorical variables, and the *t*-test for continuous variables after Bonferonni adjustment at $p < 0.001$. Other comparisons were exploratory analysis and we did not check the p-value.

Overall survival at 12 months was measured from the date of diagnosis to the last follow-up or death from any cause. For the multivariate analysis, hazard ratios and their 95% confidence intervals (95% CIs) were determined by means of the Cox regression model with shared frailty to determine factors associated with time to death. Frailties that are random effects are entered on the hazard function to model correlation within each hospital. The proportional hazard assumption was tested using weighted residuals. Clinically relevant variables with p-value <0.25 were removed following a backwards-stepwise selection procedure, leaving only variables with p-value <0.05 in the final model. Interaction terms were explored to take into account potential baseline hazards of death by hospital. Overall survival (cumulative survival probability and 95% CI) was estimated by the Kaplan–Meier method and comparisons of survival were performed by logrank tests.

The analysis took into account only cases for which the corresponding parameter was available. All variables were coded and analysed with Stata computer package version 10 (Stata Statistical Software; Stata Corporation, College Station, TX, USA).

Results

Incidence

From January 2005 to December 2007, 424 case-patients were recorded. Overall, the median incidence of IA was 0.271 per 1000 admissions (range 0.072–0.910). No significant change in the incidence was observed over time and no seasonal trend was noted. The overall incidence was 8.1% (84/1043) and 0.9% (18/2010) in allogeneic and autologous HSCT patients, respectively. Among SOT patients, the calculated IA incidence was 4.8% (7/146), 4.1% (7/172), 0.8% (9/1067) and 0.3% (11/3157) for heart, lungs, liver and kidney transplantation, respectively.

Description of the population

Out of the 424 case-patients, 31 were children (i.e. <18 years). The subsequent analyses concerned only the 393 adults (62% male patients; median age = 56 years; range, 18–84 years). Cases were classified as proven (*n* = 60, 15%) and probable (*n* = 333, 85%) IA. Overall, 305 (77.6%) patients had haematological malignancies. The main underlying risk factors/diseases were divided into eight groups (Table 1) after dispatching the patients with autologous HSCT (*n* = 19) and the HIV-positive patients (*n* = 8) according to their associated underlying disease. The major one was acute leukaemia (AL) (*n* = 136, 34.6%). Chronic lymphoproliferative disorders emerged as the second haematological underlying disease (*n* = 85, 21.6%), followed by allogeneic HSCT (*n* = 84, 21.4%). All patients with chronic lymphoproliferative disorders accounted for 35% (*n* = 106) of all haematological malignancies. Other patients had SOT (*n* = 34, 8.7%), solid tumours (*n* = 17, 4.3%), systemic inflammatory diseases with high-dose steroid therapy (*n* = 18, 4.6%), or chronic respiratory diseases (*n* = 9, 2.3%). Finally, ten (2.5%) patients had none of the above risk factors, including five with IA diagnosed at autopsy without known risk factor.

TABLE 1. Risk factors for invasive aspergillosis and underlying diseases of the 393 adult patients of the study

Risks factors/underlying diseases	*n* (%)
Acute leukaemia	136/393 (34.6)
Acute myeloid leukaemia	90/136 (66.2)
Acute lymphoid leukaemia	21/136 (15.4)
Myelodysplasia	9 (6.6)
Acute transformation	16 (11.8)
Allogeneic HSCT	84/393 (21.4)
Acute myeloid leukaemia	28 (33.3)
Acute lymphoid leukaemia	18 (21.4)
Myelodysplasia	4 (4.8)
Acute transformation	7 (8.3)
Lymphoma	13 (15.5)
Chronic lymphoid leukaemia	3 (3.6)
Multiple myeloma	5 (6.0)
Aplasia	3 (3.6)
Others	3 (3.6)
Chronic lymphoproliferative disorders	85/393 (21.6)
Lymphoma	42 (49.4)
Chronic lymphoid leukaemia	26 (30.6)
Multiple myeloma	13 (15.3)
Others	4 (4.7)
Solid organ transplantation	34/393 (8.7)
Heart	7 (20.1)
Lung	7 (20.1)
Liver	9 (26.5)
Kidney	11 (32.4)
Solid tumours	17/393 (4.3)
Broncho-pulmonary and others	6 (35.3)
Others	11 (64.7)
Systemic inflammatory diseases	18/393 (4.6)
Vasculitis	5 (27.8)
Inflammatory rheumatism	3 (16.7)
Glomerulonephritis	2 (11.1)
Others	8 (44.4)
Chronic respiratory diseases	9/393 (2.3)
Chronic obstructive pulmonary disease	2 (22.2)
Pulmonary fibrosis	4 (44.4)
Asthma	2 (22.2)
Others	1 (11.1)
None of the above risk factors	10/393 (2.5)

Main characteristics of invasive aspergillosis

For patients with AL, IA occurred for 68% (93/136) of them during the induction phase of chemotherapy, for 27% during consolidation and for 5% during palliative care. For the 85 non-allografted patients with chronic lymphoproliferative disorders, IA occurred for 27% (23/85) during the induction phase, for 67% (57/85) during malignancy relapse/non-control, and for 6% (5/85) during palliative care. The time interval between allogeneic HSCT and the occurrence of IA was <40 days, ≥40–100< and ≥100 days for 16 (19%), 11 (13%) and 57 (68%) patients, respectively. IA occurred in the first 12 weeks following heart transplantation (6/7) and at least 100 days after surgery for the other transplant procedures (18/27).

Localization of IA was mostly pulmonary (365/393, 92.9%), either isolated (324/393, 82%) or associated with other localizations (41/393, 10%) that consisted mainly of sinus (*n* = 18) and central nervous system (CNS, *n* = 20) involvement. Isolated extrapulmonary aspergillosis was documented in 28 patients (8%) and consisted of sinusitis (*n* = 11) and/or CNS localizations (*n* = 9).

Diagnostic tools and microbiological results

Imaging. Chest computed tomography (CT) scan was performed in 310 (78.9%) patients, with no significant difference according to underlying diseases. Chest nodules were found in 252/310 (81.3%) patients with pulmonary IA, associated with halo sign or cavitation in 47 (15.2%) and 126 patients (40.6%), respectively. There were 58 (18%) patients with proven or probable IA, with CT signs not reported as nodule, halo sign and/or cavitation, without a statistically significant difference according to the eight groups (Table 2).

GM serum detection. GM serum detection was performed at least twice for 345/393 (88%) patients. Despite a change in the positivity's threshold in 2006, no modification in the percentage of cases with two positive tests was noted over time (p 0.7). Two positive tests were recorded in 197/345 patients (57%), with variations ranging from 69% in AL and allogeneic HSCT to 40%, 26% and 0% in the chronic lymphoproliferative disorders, SOT and the chronic respiratory disease groups, respectively ($p < 10^4$). GM detection was performed in 91 BAL fluids and was reported positive for 43 of them (47%). GM positivity in BAL fluid (index ≥ 1.5) was the only microbiological criterion in four patients (Table 2).

Microbiological investigations. Direct examination and culture of clinical specimens were performed in 325 (82.7%) patients. Direct examination was positive in 56% (182/325), with the

TABLE 2. Characteristics, diagnostic means, treatment and outcome according to risk factors/underlying diseases in the 393 cases of invasive aspergillosis of the study

	Acute leukaemia (*n* = 136)	Allogeneic HSCT (*n* = 84)	Chronic lympho-proliferative disorders (*n* = 85)	Solid organ transplantation (*n* = 34)	Solid tumours (*n* = 17)	Systemic inflammatory diseases (*n* = 18)	Chronic respiratory diseases (*n* = 9)	Others (*n* = 10)	p[a]
Mean age (years) (95% CI)	55 (53–58)	44 (41–47)	59 (56–62)	54 (50–58)	58 (51–65)	62 (55–70)	63 (52–73)	55 (44–66)	$<10^{-3}$
Male, *n*	77 (56.6%)	56 (66.7%)	53 (62.4%)	25 (73.5%)	15 (88.2%)	6 (33.3%)	7 (77.8%)	5 (50%)	0.016
Proven IA	20 (14.7%)	11 (13.1%)	6 (7.1%)	7 (20.6%)	6 (35.3%)	4 (22.2%)	1 (11.1%)	5 (50.0%)	0.004
CT scan and chest X-ray, No. of patients examined	124 (91.2%)	71 (84.5%)	66 (77.7%)	26 (76.5%)	9 (52.9%)	13 (72.2%)	9 (100%)	6 (60%)	$<10^{-3}$
CT signs recorded in those with pulmonary IA (%)									
Nodule	104/121 (86.0%)	56/65 (86.2%)	51/65 (78.5%)	15/23 (65.2%)	5/9 (55.6%)	10/13 (76.9%)	8/9 (88.9%)	3/5 (60.0%)	0.075
With halo sign	19/121 (15.7%)	6/65 (9.2%)	8/65 (12.3%)	2/23 (8.7%)	4/9 (44.4%)	2/13 (15.4%)	3/9 (33.3%)	3/5 (60.0%)	0.008
With cavitation	66/121 (54.6%)	28/65 (43.1%)	18/65 (27.7%)	10/23 (43.5%)	0/9	2/13 (15.4%)	2/9 (22.2%)	0/5	$<10^{-3}$
Other signs	17/121 (14.1%)	9/65 (13.9%)	14/65 (21.5%)	8/23 (34.8%)	4/9 (44.4%)	3/13 (23.1%)	1/9 (11.1%)	2/5 (40.0%)	0.075
Serum positive for galactomannan detection, No. 2 positive sera/No. 2 sera tested	92/134 (68.7%)	56/81 (69.1%)	27/67 (40.3%)	8/31 (25.8%)	4/8 (50%)	4/11 (36.4%)	0/5	6/8 (75%)	$<10^{-3}$
Direct examination, No. positive/No. tested (%)	46/95 (48.4%)	30/66 (45.5%)	40/76 (52.6%)	23/34 (67.7%)	13/17 (76.5%)	14/18 (77.8%)	7/9 (77.8%)	9/10 (90%)	0.005
Positive culture, No. positive/No. tested (%)	50/95 (52.6%)	45/66 (68.2%)	67/76 (88.2%)	32/34 (94.1%)	15/17 (88.2%)	18/18 (100%)	9/9 (100%)	10/10 (100%)	$<10^{-3}$

	Acute leukaemia	Allogeneic HSCT	Chronic lympho-proliferative disorders	Solid organ transplantation	Solid tumours	Systemic inflammatory diseases	Chronic respiratory diseases	Others	p
Antifungal treatment, No. of patients treated	134	82	69	34	15	17	7	9	0.501
Voriconazole alone	74	31	44	14	11	7	5	4	
Caspofungin alone	16	14	10	6	2	2	0	0	
L-AmB alone	7	8	4	4	0	3	1	1	
Voriconazole + Caspofungin	10	9	2	4	0	0	0	3	
Voriconazole + L-AmB	4	4	3	2	0	1	0	0	
Caspofungin + L-AmB	8	4	3	1	0	1	0	0	
Others[b]	15	12	3	3	2	3	1	1	
Death within 90 days	51/135 (37.8%)	47/84 (56.0%)	35/83 (42.2%)	10/34 (29.4%)	10/15 (66.7%)	10/18 (55.6%)	4/9 (44.4%)	7/10 (70%)	0.019

L-AmB, lipid formulation of amphotericin B.

[a]The comparisons are carried out among the eight groups by use of the χ^2 test or Fisher's exact test for categorical variables, and the *t*-test for continuous variables.

[b]Others included amphotericin B deoxycholate (*n* = 16), posaconazole (*n* = 7), itraconazole (*n* = 3) alone or in combination with two or three drugs including voriconazole (six cases), caspofungin (seven cases) or L-AmB (three cases).

lowest rate in the allogeneic HSCT group (p 0.005). Culture was positive for 76% (246/325) (from 53% (50/95) for AL to >88% for the other groups ($p < 10^{-3}$)). When positive (n = 246), cultures yielded 196 *A. fumigatus* (79.7%), 11 *A. niger*, 10 *A. flavus*, seven *A. nidulans*, five *A. terreus*, five other species and 12 mixtures all including *A. fumigatus*. No non-*fumigatus* species was reported in non-haematological patients (Table 2).

Treatment

First-line therapy prescribed for at least 48 h was reported for 367 (93.4%) patients. For 26 patients, there was no prescription of antifungal therapy (autopsy findings, death before final diagnosis, palliative care). Monotherapy was prescribed for 294 (80%) patients while any combination was used in 73 (19.9%), with no significant difference according to the underlying group (Table 2).

Outcome

The outcome at day 90 was available for 388/393 (99%) patients, with death recorded in 174 patients (44.8%; 95% CI, 39.8–50.0) (Table 3). Univariate analysis identified several parameters associated with death. Thus, the proportion of older patients, those with positive culture and at least two GM positive serum samples (35.8% vs. 19.3%) and those with CNS involvement (10.9% vs. 4.7%) or pleural effusion (41.7% vs. 18.0%) was higher, while the proportion of patients receiving voriconazole either alone or in combination (54.3% vs. 75.8%) or the proportion of patients with pulmonary nodules, halo sign and/or cavitation (59.2% vs. 78.5%) was smaller when comparing the patients who died with those who survived (Table 3 and Fig. 1a,b).

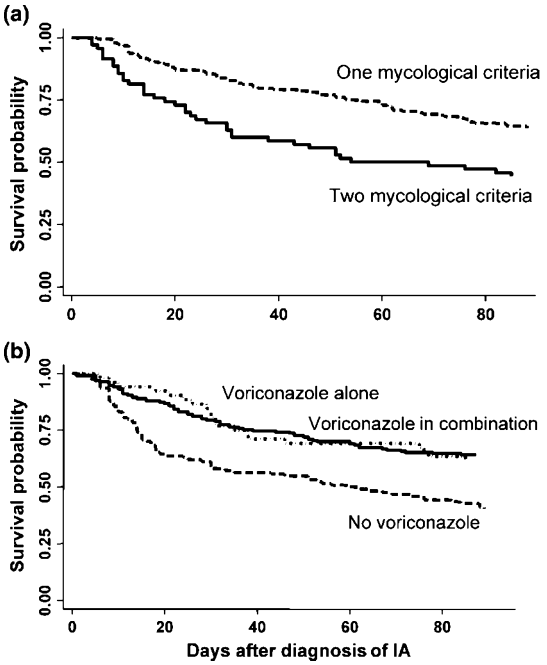

FIG. 1. Overall survival at 3 months after diagnosis of invasive aspergillosis. (a) Patients diagnosed either with one (plain line) or with at least two mycological (dashed line) criteria. (b) Patients given any antifungal regimens containing voriconazole, either alone (plain line) or in combination (dotted line), or any antifungal regimens without voriconazole (dashed line).

In the multivariate analysis, after taking into account the within-hospital correlation, the parameters independently associated with an increased risk of death were an older age, a diagnosis based on positive culture together with two positive GM detections in serum samples, the presence of pleural

TABLE 3. Parameters associated with deaths within 90 days after the diagnosis of IA for the 388/393 adult patients for whom the outcome was available

	Univariate analysis			Multivariate analysis	
Parameters	No. deaths (n = 214)	Deaths before day 90 (n = 174)	p	OR (95% CI)	p
Gender male	135/214 (63.1%)	106/174 (60.9%)	0.675		
Median age (IC 95%)	52.5 (50.5–54.5)	55.7 (53.5–58.0)	0.034	1.02 (1.00–1.03)	0.034
Underlying risk factors					
Acute leukaemia	84 (38.3%)	51 (29.3%)	0.018		
Allogeneic graft	37 (17.3%)	47 (27.0%)			
Lymphoid disorders	48 (22.4%)	35 (20.1%)			
Solid organ transplantation	24 (11.2%)	10 (5.8%)			
Solid tumours	5 (2.3%)	10 (5.8%)			
Systemic	8 (3.7%)	10 (5.8%)			
Chronic respiratory	5 (2.3%)	4 (2.3%)			
Others	3 (1.4%)	7 (4.0%)			
Positive culture and positive galactomannan on ≥2 serum samples	29/150 (19.3%)	39/109 (35.8%)	0.004	1.72 (1.07–2.74)	0.023
Central nervous system involvement	10/214 (4.7%)	19/174 (10.9%)		2.01 (1.04–3.90)	0.039
Pleural effusion	34/189 (18.0%)	55/132 (41.7%)	$<10^{-3}$	2.38 (1.53–3.70)	$<10^{-3}$
Presence of nodule, halo sign and/or cavitation	155/197 (78.7%)	97/164 (59.2%)	$<10^{-3}$		
Initial antifungal treatment including voriconazole	150/198 (75.8%)	89/164 (54.3%)	$<10^{-3}$	0.53 (0.34–0.82)	0.005

effusion or CNS involvement, while an initial antifungal treatment including voriconazole (alone or in combination) was associated with a decreased risk of death (Table 3).

Discussion

The incidence of IA was 0.271/1000 admissions, from 0.072 to 0.91 according to the hospital, without any significant temporal trend or any seasonal influence. The different recruitment of the participating hospitals and obvious differences in clinical approaches to IA diagnosis, which will be further analysed, may explain these differences.

As expected, haematological malignancies provided the highest proportion of IA. Surprisingly, 35% of haematological-associated IA occurred in patients with chronic lymphoproliferative disorders, with 67% occurring during second-line therapies. Studies focused on this population could support our results, which suggest an intensifying treatment or the cumulative immune suppression as a possible cause of increased risk of IA in this specific group [1]. When considering the subpopulations, the incidence was 8.1% among allogeneic HSCT recipients, which is within the range of previous reports [13–15]. Of note, 70% occurred >100 days after the graft, as underlined by others [12,13] although not always reported [14]. For autologous HSCT, the 0.9% incidence is concordant with other data [12,14,16].

The incidence of IA according to the transplant procedure was in the range previously recorded [4], with a late occurrence after lungs, liver or kidney transplantation. HIV infection dramatically decreased (2%) compared with previous reports [16,17]. IA was recorded in non-haematology cancer patients, systemic inflammatory or chronic respiratory diseases and some other conditions in up to 15% of the population, higher than previously reported [16,17]. In these latter patients, we evidenced the low yield of serum GM detection. GM contribution depends on the likelihood of IA occurrence [18] and on previous antifungal therapy [19]. Another plausible explanation would be the pathophysiology of IA in deeply neutropenic patients vs. patients receiving prolonged steroid therapy [20]. Indeed, lymphoproliferative diseases correspond to patients for whom neutropenia is not the predominant risk factor [21]. The poor performance of serum GM in non-neutropenic patients and the difficulty in fulfilling the clear-cut CT-scan criteria in intensive care unit patients [11] underline the need for refining diagnostic criteria for these populations [6]. This underlines also the interest of the main mycological criterion of the present study, which remains a positive culture [22]. Also of note was the high rate (56%) of positive direct examination.

Twelve-week overall mortality was 44.8%, with differences between groups, similar to a report of 48.8% in a single-centre study [2]. For AL, the present mortality rate was 37.8%, a figure close to the 33% recently reported [23]. For allogeneic HSCT recipients, our 56% overall mortality is close to the 57.5% rate in the TRANSNET study [24] but by far higher than the 35.5% reported in the PATH Alliance registry [12]. Nevertheless, the mortality rate is lower than the 66% previously observed, suggesting a substantial improvement of IA prognosis in the allogeneic HSCT recipients [25]. In SOT patients, the mortality rate found here is concordant with the TRANSNET study (29.4% and 34.4%, respectively) [24].

Independent factors associated with death were here an older age, the combination of two positive GM tests and a positive microbiological investigation, and the involvement of pleura and/or CNS. If involvement of pleura or CNS has previously been identified as a prognostic factor [2,25,26], it is not the case for the combination of the biological diagnostic tools. This could be explained by a more advanced disease with a larger fungal burden. This emphasizes the importance of individualizing patients with unique or multiple positive tests in future clinical trials. In contrast, CT-scan signs suggestive of pulmonary IA were associated with a better prognosis, which was potentially ascribed to an earlier diagnosis [27].

Voriconazole represented the main first-line therapy prescription (51.8% of cases) while amphotericin B deoxycholate has almost disappeared. Caspofungin and antifungal combinations represented 14% and 17% of the first-line therapy prescriptions, with an increase or decrease in use over time, respectively. Of note, combination therapy was reported in 47.2% of HSCT patients [12] despite lack of benefit in this population [24] and lack of recommendation [28].

Interestingly, although not obtained during a randomized trial but taking into account variations in relation to the hospital, the use of any strategy using voriconazole was an independent factor for survival. The 90-day survival rates were 59% and 40% in voriconazole-treated and non-treated patients, respectively. These data are reminiscent of those reported in the pivotal voriconazole trial (70.8% and 57.9% in the voriconazole and amphotericin B groups, respectively) [29].

In conclusion, this prospective multicentre surveillance study allowed us to demonstrate that IA incidence markedly varied according to clinical centres. An emergence of IA in patients with heavily treated chronic lymphoproliferative disorders was recorded. Among the other major issues, the poor contribution of serum GM in all non-haematology groups, the need to better assess fungal burden by combining

fungal culture and serum antigen detection and the role of voriconazole as first-line therapy are emphasized.

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Transparency Declaration

O.L. is consultant for FAB Pharma, Gilead Sciences and Astellas, and a member of the speaker's bureau of Pfizer, MSD, Astellas and Gilead Sciences. J-P.G. is a member of advisory boards and/or received grant support from Astellas, Gilead, MSD, Pfizer and Schering-Plough. S.B. is consultant for Gilead Sciences, has received speaking honoraria from Pfizer and Gilead Sciences and travel grants from Astellas, Pfizer and Schering-Plough. K.S., B.L., F.M., Y. LS., B.C. and F.D.: no conflict of interests.

Appendix

SAIF study group members

Felipe Suarez, Nizar Mahlaoui, Marie-Elisabeth Bougnoux, Olivier Lortholary (Necker Hospital); Jean-Louis Poirot, Françoise Isnard (Saint Antoine Hospital); Eric Dannaoui, Romain Guillemain (Hôpital Européen Georges Pompidou); Catherine Cordonnier, Cécile Pautas, Yosr Hicheri, Françoise Foulet, Stéphane Bretagne (Chenevier-Mondor Hospital); Claire Lacroix, Patricia Ribaud, Anne Bergeron, Juliette Pavie, Emmanuel Raffoux, Benoit Brethon (Saint Louis Hospital); Dorothée Quinio, Elodie Moalic, Francis Coutureau, Gaelle Guillerm (Centre Hospitalo-Universitaire de Brest); Marguerite Fines-Guyon, Renaud Verdon (Centre Hospitalo-Universitaire de Caen); Françoise Gay-Andrieu, Philippe Moreau, Philippe Tallarmin (Centre Hospitalo-Universitaire de Nantes); Jean-Pierre Gangneux, Sylviane Chevrier, Christophe Camus, Sophie de Guibert, Matthieu Revest (Centre Hospitalo-Universitaire de Rennes); Jacques Chandenier, Eric Bailly, Frédéric Bastides (Centre Hospitalo-Universitaire de Tours); Bernadette Lebeau, Marie Pierre Brenier-Pinchart, Marie Reine Mallaret, Rebecca Hamidfar, Annick Bosseray, Frédérick Garban (Centre Hospitalo-Universitaire de Grenoble); Frédérique de Monbrison, Anne Thiébaut, Marie Christine Nicolle, Mauricette Michallet (Hôpitaux Civils de Lyon).

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