

## Improvement in the outcome of invasive fusariosis in the last decade

M. Nucci<sup>1</sup>, K. A. Marr<sup>2</sup>, M. J. G. T. Vehreschild<sup>3</sup>, C. A. de Souza<sup>4</sup>, E. Velasco<sup>5</sup>, P. Cappellano<sup>6</sup>, F. Carlesse<sup>7</sup>, F. Queiroz-Telles<sup>8</sup>, D. C. Sheppard<sup>9</sup>, A. Kindo<sup>10</sup>, S. Cesaro<sup>11</sup>, N. Hamerschlag<sup>12</sup>, C. Solza<sup>13</sup>, W. J. Heinz<sup>14</sup>, M. Schaller<sup>15</sup>, A. Atalla<sup>16</sup>, S. Arikan-Akdagli<sup>17</sup>, H. Bertz<sup>18</sup>, C. Galvão Castro Jr<sup>12</sup>, R. Herbrecht<sup>19</sup>, M. Hoenigl<sup>20</sup>, G. Härter<sup>21</sup>, N. E. U. Hermansen<sup>22</sup>, A. Josting<sup>23</sup>, L. Pagano<sup>24</sup>, M. J. C. Salles<sup>25</sup>, S. B. Mossad<sup>26</sup>, D. Ogunc<sup>27</sup>, A. C. Pasqualotto<sup>28</sup>, V. Araujo<sup>29</sup>, P. F. Troke<sup>30</sup>, O. Lortholary<sup>31</sup>, O. A. Cornely<sup>3,32</sup> and E. Anaissie<sup>33</sup>

1) University Hospital, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, 2) Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA, 3) First Department of Internal Medicine, University Hospital Cologne, Cologne, Germany, 4) Haematology and Chemotherapy Centre, University of Campinas (UNICAMP), Campinas, Brazil, 5) National Cancer Institute, Rio de Janeiro, 6) University Hospital, Federal University of São Paulo (UNIFESP), 7) Institute of Paediatric Oncology (GRAACC), Federal University of São Paulo (UNIFESP), São Paulo, 8) University Hospital, Federal University of Paraná (UFPR), Curitiba, Brazil, 9) Departments of Medicine & Microbiology and Immunology, McGill University, Montreal, Canada, 10) Department of Microbiology, Sri Ramachandra Medical College/Research Institute, No. 1, Chennai, India, 11) Oncoematologia Pediatrica, Policlinico G. B. Rossi, Verona, Italy, 12) Hospital Albert Einstein, São Paulo, 13) Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil, 14) Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany, 15) Universitäts-Hautklinik Tübingen, Uniklinik Tübingen, Germany, 16) Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil, 17) Department of Medicine, Section of Infectious Diseases, Hacettepe University Medical School, Ankara, Turkey, 18) Hämatologie und Onkologie, Universitätsklinikum Freiburg, Freiburg, Germany, 19) Hôpital de Haute-pierre, Strasbourg, France, 20) Department of Medicine, Medical University of Graz, Graz, Austria, 21) Comprehensive Infectious Diseases Centre (CIDC), Ulm, Germany, 22) Department of Haematology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark, 23) Hämatonkologie, Gastroenterologie und Palliativmedizin, OnkoBer, Berlin, Germany, 24) Dipartimento di Ematologia, Università Cattolica del Sacro Cuore, Rome, Italy, 25) Santa Casa of São Paulo School of Medicine, São Paulo, Brazil, 26) Section of Transplant Infectious Diseases, Department of Infectious Diseases, Medicine Institute and Transplant Center, Cleveland Clinic Lerner College of Medicine of Case Western University, Cleveland, OH, USA, 27) Department of Clinical Microbiology, Akdeniz University Medical Faculty, Antalya, Turkey, 28) Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, 29) Hospital Governador Celso Ramos, Florianópolis, Brazil, 30) The Old Court, Broadstairs, Kent, UK, 31) Unité de Mycologie Moléculaire, Institut Pasteur, Centre National de Référence Mycologie et Antifongiques, Paris, France, 32) Clinical Trials Centre Cologne (ZKS Köln, BMBF 01KN1106) University of Cologne, Cologne, Germany and 33) Division of Hematology and Oncology, University of Cincinnati, Cincinnati, OH, USA

### Abstract

Invasive fusariosis (IF) has been associated with a poor prognosis. Although recent series have reported improved outcomes, the definition of optimal treatments remains controversial. The objective of this study was to evaluate changes in the outcome of IF. We retrospectively analysed 233 cases of IF from 11 countries, comparing demographics, clinical findings, treatment and outcome in two periods: 1985–2000 (period 1) and 2001–2011 (period 2). Most patients (92%) had haematological disease. Primary treatment with deoxycholate amphotericin B was more frequent in period 1 (63% vs. 30%,  $p < 0.001$ ), whereas voriconazole (32% vs. 2%,  $p < 0.001$ ) and combination therapies (18% vs. 1%,  $p < 0.001$ ) were more frequent in period 2. The 90-day probabilities of survival in periods 1 and 2 were 22% and 43%, respectively ( $p < 0.001$ ). In period 2, the 90-day probabilities of survival were 60% with voriconazole, 53% with a lipid formulation of amphotericin B, and 28% with deoxycholate amphotericin B ( $p < 0.04$ ). Variables associated with poor prognosis (death 90 days after the diagnosis of fusariosis) by multivariable analysis were: receipt of corticosteroids (hazard ratio (HR) 2.11, 95% CI 1.18–3.76,  $p < 0.01$ ), neutropenia at end of treatment (HR 2.70, 95% CI 1.57–4.65,  $p < 0.001$ ), and receipt of deoxycholate amphotericin B (HR 1.83, 95% CI 1.06–3.16,  $p < 0.03$ ). Treatment practices have changed over the last decade, with an increased use of voriconazole and combination therapies. There has been a 21% increase in survival rate in the last decade.

**Keywords:** Epidemiology, fusariosis, outcome, treatment, voriconazole

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**Corresponding author:** M. Nucci, MD, University Hospital, Universidade Federal do Rio de Janeiro. Rua Prof. Rodolpho Paulo Rocco 255 Sala 4A 12, Rio de Janeiro 22251-030, Brazil  
**E-mail:** mnucci@hucff.ufrj.br

## Introduction

Invasive fusariosis (IF) is a leading mycosis affecting immunocompromised patients [1]. The disease is usually invasive and disseminated, affecting mostly neutropenic patients with acute leukaemia [2] or patients with severe T-cell immunodeficiency, especially haematopoietic cell transplant recipients receiving corticosteroids for the treatment of severe graft-versus-host disease (GVHD) [3]. Most infections in humans are caused by *Fusarium solani* species complex and *Fusarium oxysporum* species complex [1].

The treatment of IF is limited by the fact that most *Fusarium* species show high MICs for the antifungal agents available, including the extended-spectrum azoles voriconazole and posaconazole [1]. The previously reported prognosis of IF in immunocompromised patients is very poor, with 90-day survival rates of only 21% in patients with haematological malignancies [2] and 13% in haematopoietic cell transplant recipients [3]. However, recent data have suggested that the outcome of IF has improved [4,5].

In this study, we analysed a large series of cases of IF, encompassing patients diagnosed between 1985 and 2011, to determine whether the outcome of IF has indeed improved. We also sought to identify changes in the epidemiology, clinical presentation, diagnostic procedures, and therapeutic practices, and to identify predictors of poor outcome.

## Methods

This was a retrospective analysis of cases of IF from different parts of the world. Four databases were merged: the first database collected cases of IF from 12 Brazilian centres and two centres in the USA; the second (FungiScope—A Global Registry for Emerging Fungal Infections) collected cases from different parts of the world; the third collected data from the Pfizer voriconazole clinical database; and the fourth collected cases from the French National Reference Centre for Invasive Mycoses and Antifungals [5]. The study was approved by the Ethics Committee of participating centres. A case report form was designed in order to accommodate differences in the original databases. Three authors (M.J.G.T.V., P.F.T., and M.N.) reviewed the definitions of each variable contained in the original databases, in order to ensure consistency in the process of merging. We collected data regarding demographics, underlying disease and its treatment, details of haematopoietic cell transplantation, including donor type, stem cell source, the presence and severity of GVHD, and receipt of corticosteroids (in the 15 days preceding the diagnosis of IF),

neutropenia ( $<500/\text{mm}^3$ ), clinical manifestations of IF, diagnosis, the species causing infection, treatment, and outcome (90-day survival). Disseminated fusariosis was defined as the involvement of more than one non-contiguous organ. Cases of fungaemia were not defined as disseminated disease unless another organ was involved (e.g. skin, lung, or sinuses).

All cases were reviewed by one of the authors (M.N.) blinded to treatment and time period, and classified as proven or probable IF according to the modified European Organization for Treatment and Research of Cancer/Mycosis Study Group criteria [6]. Cases of possible fusariosis and of non-invasive infection were excluded.

For the purpose of this analysis, we arbitrarily established two time periods: 1985–2000 (period 1) and 2001–2011 (period 2). Demographics, underlying diseases and their treatment, neutropenia, receipt of corticosteroids, clinical manifestations, diagnostic procedures, treatment and outcome (90-day survival) were compared over the two periods. In addition, we assessed factors associated with 90-day survival in period 2, to evaluate the effects of different treatments on the outcome. For this analysis, cases in which no treatment was given were excluded. The following variables were evaluated by univariate and multivariable Cox regression analysis: age, gender, country (Brazil vs. others and USA vs. others), underlying disease, receipt of corticosteroids, neutropenia at diagnosis of fusariosis and at end of treatment, clinical manifestations, and primary treatment (deoxycholate amphotericin B, lipid amphotericin B, voriconazole, or combination treatment). Variables with a p-value of  $<0.1$  by univariate analysis were entered into the multivariable analysis, and variables with a p-value of  $<0.05$  were maintained in the final model.

Categorical variables were compared by use of the chi-square or Fisher exact test as appropriate, and continuous variables were compared by use of the Wilcoxon test. Kaplan–Meier curves were constructed and compared by use of the log-rank test. p-Values of  $<0.05$  were considered to be statistically significant, and all statistical tests were performed with SPSS software (SPSS, version 16.0; SPSS, IBM Inc., New York, NY, USA).

## Results

A total of 233 cases were recorded from 44 centres in 11 countries: Brazil ( $n = 124$ ), the USA ( $n = 69$ ), Germany ( $n = 13$ ), Canada, Italy and India (five each), France ( $n = 4$ ), Turkey ( $n = 3$ ), Austria ( $n = 2$ ), Switzerland, England, and Denmark (one each). There were 121 cases diagnosed in period 1 (1985–2000) and 112 in period 2 (2001–2011). Table 1 shows the baseline characteristics of patients.

Species identification was available locally in 49 of the 233 cases (23%). *F. solani* species complex was the most frequent agent ( $n = 29$ ), followed by *F. oxysporum* species complex ( $n = 7$ ), *Fusarium incarnatum* and *Fusarium proliferatum* (three cases each), *Fusarium verticillioides* ( $n = 3$ ), and *Fusarium dimerum*, *Fusarium sacchari*, *F. solani* + *Fusarium antophilium* and *Fusarium sporotrichoides* (one case each).

Skin involvement was observed in 61% of patients, and its frequency did not differ over the two periods (58% in period 1 and 65% in period 2,  $p = 0.25$ ; Table 2). Detailed information on the diagnostic method was available in 224 of the 233 cases. The diagnosis was made by culture alone in 138 cases, culture plus histopathology in 83, and histopathology alone in three (probable fusariosis). The skin was the most frequent source of diagnosis (100 cases), followed by the blood (85 cases). Histopathological confirmation of disease was more frequent in period 2 (47 vs. 29%,  $p = 0.006$ ).

**TABLE 1. Baseline characteristics of 233 patients with invasive fusariosis**

Characteristic	Total, N = 233	Period 1, N = 121	Period 2, N = 112	p-Value
Gender: male/female	147 : 86	68 : 53	79 : 33	0.02
Age (years), median (range)	39.5 (2–76)	33 (2–76)	44 (3–75.5)	0.003
Underlying disease				
Haematological disease	215 (92)	115 (95)	100 (89)	0.10
Acute myeloid leukaemia	91 (39)	44 (36)	47 (42)	
Acute lymphoid leukaemia	46 (20)	22 (18)	24 (21)	
Chronic myeloid leukaemia	22 (9)	18 (15)	4 (4)	
Myelodysplastic syndrome	13 (6)	8 (7)	5 (4)	
Aplastic anaemia	13 (6)	7 (6)	6 (5)	
Non-Hodgkin lymphoma	11 (5)	7 (6)	4 (4)	
Multiple myeloma	10 (4)	5 (4)	5 (4)	
Myelofibrosis	1 (1)	–	1 (1)	
Solid tumour	6 (3)	2 (2)	4 (4)	
Solid organ transplantation <sup>a</sup>	3 (1)	1 (1)	2 (2)	
Other <sup>b</sup>	9 (4)	3 (2)	6 (5)	
HCT	104 (45)	62 (51)	42 (37)	0.03
Autologous	15/104 (14)	7/62 (11)	8/42 (19)	
Allogeneic	89/104 (86)	55/62 (89)	34/42 (81)	
Donor relatedness				
Related	57/89 (64)	36/55 (65)	21/34 (62)	0.72
Unrelated	32/89 (36)	19/55 (34)	13/34 (38)	
HLA match				
Matched	83/89 (93)	50/55 (91)	33/34 (97)	0.40
Mismatched	6/89 (7)	5/55 (9)	1/34 (3)	
Acute GVHD III/IV	21/89 (24)	15/55 (27)	6/34 (18)	0.30
Chronic extensive	11/89 (12)	8/55 (14)	3/34 (9)	0.52
GVHD				
Receipt of corticosteroids <sup>c</sup>	119/228 (52)	56/116 (48)	63/112 (56)	0.23
Neutropenia at diagnosis of fusariosis	176 (75)	80 (66)	96 (86)	0.001
Neutropenia at end of treatment	88 (38)	51 (42)	37 (33)	0.15

Numbers in parentheses represent percentages unless otherwise specified. GVHD, graft-versus-host disease; HCT, haematopoietic cell transplantation; HLA, human leukocyte antigen.

<sup>a</sup>Solid organ transplantation: kidney (three patients).

<sup>b</sup>Other underlying diseases: multiple sclerosis (three patients), diabetes, asthma, stroke, hepatitis B, chronic use of corticosteroids, and leukodystrophy (one patient each).

<sup>c</sup>Information not available for five patients.

A total of 206 patients (88%) received treatment for fusariosis, with a higher proportion of patients receiving treatment in period 2 (93 vs. 84%,  $p = 0.04$ ). The most frequent drug used as primary treatment was deoxycholate amphotericin B (47%), followed by voriconazole monotherapy (16%), and a lipid formulation of amphotericin B monotherapy (15%). Combination therapy was used in 21 patients: voriconazole plus a lipid formulation of amphotericin B ( $n = 12$ ), plus deoxycholate amphotericin B ( $n = 5$ ), plus terbinafine ( $n = 2$ ), and a lipid formulation of amphotericin B plus posaconazole ( $n = 2$ ). On comparison of the two periods, there was a significant reduction in the use of deoxycholate amphotericin B as primary treatment and an increase in the use of voriconazole and combination therapy (Table 2). After period had been controlled for, primary treatment did not differ significantly by centre or country.

The primary treatment regimen was modified in 47 of the 206 patients (23%) who received treatment: 8% in period 1 and 37% in period 2 ( $p < 0.001$ ). The most frequent reason for change in the primary treatment regimen was no response (38%), followed by renal toxicity (21%, all with deoxycholate amphotericin B).

As shown in Fig. 1, the 90-day probabilities of survival were 43% in period 2 and 22% in period 1 ( $p < 0.001$ ). Fig. 2 shows the 90-day probability of survival in period 2 by primary treatment: the 90-day survival rates were 60% with vorico-

**TABLE 2. Clinical manifestations and treatment of 233 patients with invasive fusariosis**

Characteristic	Total, N = 233	Period 1, N = 121	Period 2, N = 112	p-Value
Skin involvement	143 (61)	70 (58)	73 (65)	0.25
Lung involvement	114 (49)	60 (50)	54 (48)	0.83
Sinusitis	72 (31)	34 (28)	38 (34)	0.34
Fungaemia	86 (37)	31 (26)	55 (49)	<0.001
Disseminated disease	166 (72)	89 (74)	77 (69)	0.48
Received treatment	206 (88)	102 (84)	104 (93)	0.04
Deoxycholate amphotericin B	110 (47)	76 (63)	34 (30)	<0.001
Lipid formulation of amphotericin B <sup>a</sup>	34 (15)	22 (18)	12 (11)	0.11
Voriconazole	38 (16)	2 (2)	36 (32)	<0.001
Combination therapy <sup>b</sup>	21 (9)	1 (1)	20 (18)	<0.001
Other <sup>c</sup>	3 (1)	1 (1)	2 (2)	
Receipt of G-CSF or GM-CSF <sup>d</sup>	106 (47)	45 (37)	59 (53)	0.02
Granulocyte transfusion <sup>d</sup>	28 (12)	20 (16)	8 (7)	0.03

Numbers in parentheses represent percentages.

G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.

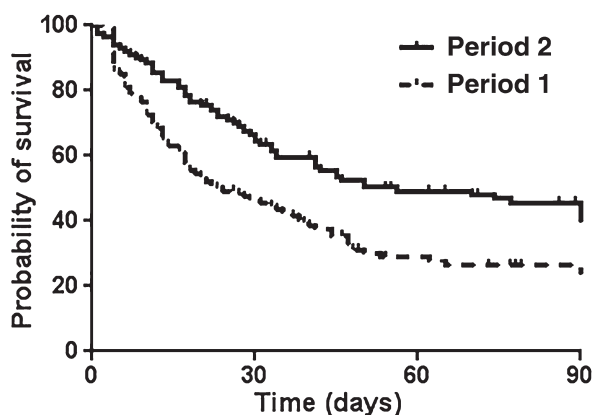
<sup>a</sup>Lipid formulation of amphotericin B: liposomal amphotericin B ( $n = 20$ ; 11 in period 1 and nine in period 2), amphotericin B lipid complex ( $n = 8$ ; six in period 1 and two in period 2), and amphotericin B colloidal dispersion ( $n = 6$ ; five in period 1 and one in period 2).

<sup>b</sup>Combination therapy consisted of voriconazole (19 cases) plus liposomal amphotericin B ( $n = 10$ ), deoxycholate amphotericin B ( $n = 5$ ), amphotericin B lipid complex ( $n = 2$ ) and terbinafine ( $n = 2$ ), and posaconazole plus liposomal amphotericin B ( $n = 1$ ).

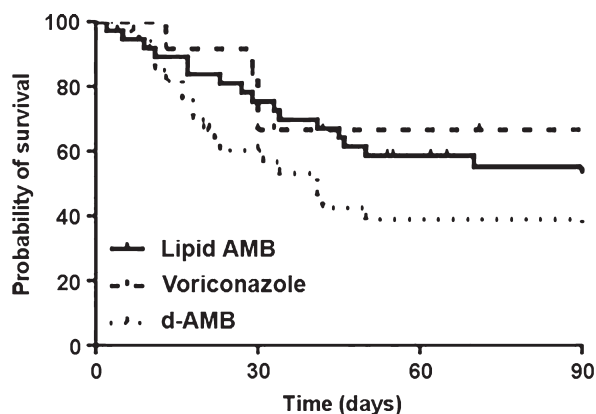
<sup>c</sup>Other treatment: itraconazole (one case, period 1), posaconazole and surgery (one case each, period 2).

<sup>d</sup>After the diagnosis of fusariosis.

nazole (95% CI 52–68), 53% with a lipid formulation of amphotericin B (95% CI 37–72), and 28% with deoxycholate amphotericin B (95% CI 20–36) ( $p$  0.04; log-rank test for trend). In the assessment of prognostic factors, variables not significant by univariate analysis were age, gender, country, presence and severity of GVHD, neutropenia at diagnosis of fusariosis, clinical presentation, and primary treatment with a lipid formulation of amphotericin B or with combination therapy. As shown in Table 3, the variables significantly associated with poor prognosis (death 90 days after the diagnosis of fusariosis) by multivariable analysis were: receipt of corticosteroids (hazard ratio (HR) 2.11, 95% CI 1.18–3.76,  $p$  0.01), neutropenia at end of treatment (HR 2.70, 95% CI 1.57–4.65,  $p$  <0.001), and receipt of deoxycholate amphotericin B (HR 1.83, 95% CI 1.06–3.16,  $p$  0.03).



**FIG. 1.** Probability of 90-day survival of 233 patients with invasive fusariosis in period 1 (1985–2000) and period 2 (2001–2011).



**FIG. 2.** Probability of 90-day survival of 83 patients with invasive fusariosis in period 2 treated with deoxycholate amphotericin B (d-AMB), voriconazole, or a lipid formulation of amphotericin B (Lipid AMB).

## Discussion

To the best of our knowledge, this is the largest series of cases of IF ever reported, with data being collected by investigators from 11 countries. We confirmed our hypothesis that the outcome of IF has improved in the last decade. We also confirmed that two host factors, i.e. receipt of corticosteroids and persistent neutropenia, are important predictors of poor outcome. In addition, we observed important changes in therapeutic practices, with a reduction in the use of deoxycholate amphotericin B and an increase in the use of voriconazole and combination therapy. Finally, primary treatment with either voriconazole or a lipid formulation of amphotericin B was associated with better outcome, whereas deoxycholate amphotericin B primary treatment was associated with poor outcome.

Overall, the clinical presentation of IF was not different in the two periods. Fungaemia was more common in period 2, possibly as a reflection of improvements in blood culture systems and media. The diagnostic practices did not change substantially over time, with the exception of a higher proportion of patients with a histopathological diagnosis in period 2. Clinicians might have become more aware of the typical clinical presentation of IF in severely immunosuppressed haematological patients [7], and the importance of obtaining tissue (mostly biopsy of skin lesions) to establish the diagnosis as early as possible. This could have contributed to the improved survival observed in period 2.

The most striking difference between periods 1 and 2 was in the choice of primary treatment regimen, with a reduction in the use of deoxycholate amphotericin B and an increase in voriconazole and combination therapy (voriconazole in all but

**TABLE 3.** Factors associated with poor outcome (death 90 days after diagnosis) in 206 patients with invasive fusariosis who received treatment

Variable	Unadjusted		Adjusted	
	HR (95% CI)	p	HR (95% CI)	p
Haematological disease	5.70 (0.79–41.24)	0.08	5.26 (0.71–38.73)	0.11
Receipt of corticosteroids	2.21 (1.24–3.94)	0.007	2.11 (1.18–3.76)	0.01
Neutropenia at end of treatment	2.61 (1.52–4.46)	<0.001	2.70 (1.57–4.65)	<0.001
Disseminated disease	1.72 (0.90–3.26)	0.09	1.45 (0.72–2.94)	0.30
Primary treatment with deoxycholate amphotericin B <sup>a</sup>	1.75 (1.02–3.01)	0.04	1.83 (1.06–3.16)	0.03
Primary treatment with voriconazole <sup>a</sup>	0.61 (0.34–1.11)	0.09	0.77 (0.38–1.55)	0.47

HR, hazard ratio.

<sup>a</sup>As a single agent. Neither lipid amphotericin B (HR 0.67, 95% CI 0.27–1.69) or combination therapy (HR 1.20, 95% CI 0.63–2.28) was significant by univariate analysis.

one case). This increased use of voriconazole in primary treatment (especially monotherapy) is of particular interest, because *in vitro* data indicate that most *Fusarium* species (especially *F. solani*, the most frequent agent of IF) show high MICs for voriconazole [1,8,9]. In a previous study, the MIC range and geometric mean of 22 *F. solani* and 14 *F. oxysporum* isolates were 4–16 mg/L and 14 mg/L, and 0.5–16 mg/L and 4 mg/L, respectively. By contrast, amphotericin B showed better *in vitro* activity, with geometric means of 1.33 mg/L for *F. solani* and 0.78 mg/L for *F. oxysporum* [10]. Therefore, even though we acknowledge that a correlation between MIC and outcome has not been evaluated in IF, we would expect clinicians to choose a lipid formulation of amphotericin B as primary treatment, as generally recommended [11]. In our study, information on *in vitro* susceptibility was available for only 20 patients. Furthermore, as we did not have information on the laboratory procedures for MIC assessment in the different centres, we did not analyse the correlation between *in vitro* data and outcome.

The improvement in outcome of IF in period 2 may be a reflection of better management of the underlying disease, including supportive care and primary treatment [12,13]. Because of these potential differences in patient care in periods 1 and 2, we decided to evaluate prognostic factors only in period 2. Our multivariable analysis confirmed the influence of host factors (persistent neutropenia and receipt of corticosteroids) as strong predictors of poor outcome in IF [2,3]. The other significant variable was primary treatment with deoxycholate amphotericin B. By contrast, although receipt of voriconazole or a lipid formulation of amphotericin B as primary treatment was not significant in the multivariable analysis, the outcome with these drugs was better (60% and 53%, respectively) than with deoxycholate amphotericin B (28%). This 60% 90-day survival with voriconazole monotherapy as first-line treatment is remarkable, and contrasts with *in vitro* antifungal susceptibility tests, which consistently show high MICs with the majority of *Fusarium* species [10].

Our study shares the limitations of other retrospective studies. Although we were successful in merging four databases, data on some important variables were not available for all patients, including the status of the underlying disease, recent chemotherapeutic regimen, dose of corticosteroids, duration of neutropenia, pattern of lung involvement, portal of entry, and dose of antifungal treatment. However, by renouncing completeness, we were able to collect a large number of patients with IF. In addition, none of the variables included in the Cox regression analysis of predictors of poor outcome had missing values. Another potential limitation is that we did not have information on changes in patient care that could have influenced the results favouring period 2, such as improve-

ments in the management of the underlying conditions and different doses of corticosteroids for the management of GVHD.

Despite these limitations, our findings have important implications. First, as host factors are important prognostic factors, a great effort should be made to minimize and/or abbreviate immunosuppression, including neutropenia and the use of corticosteroids. Second, considering the good response with voriconazole as first-line treatment, this drug should be added to a lipid formulation of amphotericin B as an option in the primary treatment of IF. Finally, studies are needed to determine whether there is any correlation between MIC and outcome.

In conclusion, therapeutic practices have changed substantially over the last decade, with a decrease in the use of deoxycholate amphotericin B and an increase in voriconazole and combination therapy. The outcome of IF has significantly improved in the last decade.

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## Transparency Declaration

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grants from Pfizer; MH: research grants and lecture honoraria from Astellas and Merck; LP: lecture honoraria from Gilead, Merck, Pfizer and Astellas; ACP: research grants and lecture honoraria from Pfizer, Gilead, Merck and Astellas; PFT was previously an employee of and subsequently a consultant to Pfizer; OL: research grants from Merck, consultant to Merck, Astellas and Gilead, and lecture honoraria from Gilead; OC: support from the German Federal Ministry of Research and Education, research grants from 3M, Actelion, Astellas, Basilea, Bayer, Biocryst, Celgene, Cubist, F2G, Genzyme, Gilead, GSK, Merck, Miltenyi, Optimer, Pfizer, Quintiles, and Viropharma, consultant to 3M, Astellas, Basilea, Cubist, F2G, Gilead, GSK, Merck, Optimer and Pfizer, and lecture honoraria from Astellas, Gilead, Merck and Pfizer. CAS, EV, PC, FC, AK, NH, CS, MS, AA, CGCJr, GH, NEUH, AJ, MJCS, SBM, DO, VA, EA: no conflicts.

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