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Article type : Original Paper

Fungemia in hematological malignancies: SEIFEM-2015 survey

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/eci.13083

ABSTRACT

Background: Fungal infections are still a relevant challenge for clinicians involved in the cure of patients with cancer. We retrospectively reviewed charts of hospitalized patients with hematological malignancies (HMs), in which a documented fungemia was diagnosed between January 2011 and December 2015 at 28 adult and 6 pediatric Italian Hematology Departments.

Methods: During the study period we recorded 215 fungal blood stream infections (BSI). Microbiological analyses documented that BSI was due to molds in 17 patients (8%) and yeasts in 198 patients (92%), being *Candida spp* identified in 174 patients (81%).

Results: Mortality rates were 70% and 39% for mold and yeast infections, respectively. Infection was the main cause of death in 53% of the mold and 18% of the yeast groups. At the multivariate analysis, ECOG ≥2 and septic shock were significantly associated with increased mortality, and removal of CVC survival was found to be protective. When considering patients with candidemia only, ECOG ≥2 and removal of CVC were statistically associated with overall mortality.

Conclusions: Although candidemia represents a group of BSI with a good prognosis, its risk factors largely overlap with those identified for all fungemias, even though the candidemia-related mortality is lower when compared to other fungal BSI. Management of fungal BSI is still a complex issue, in which both

patients and disease characteristics should be focused to address a personalized approach.

Keywords: candidemia, fungemia, acute leukemias

INTRODUCTION

Fungal infections are still a relevant challenge for clinicians involved in the cure of patients with cancer. On one hand, high dose chemotherapy, mucosal barriers damage, impairment of immune system due to underlying malignancy and its treatment are known risk factors that are difficult to overcome. On the other hand, in this setting the wide use of antimicrobic prophylaxis and therapy as well as the preemptive antifungal treatment may have contributed to the epidemiology of identified isolates in this setting of patients.

In the last years, several studies have reported on prevalence of invasive fungal infections (IFI), defined as involvement of lung, central nervous system, sinuses and bloodstream infections (BSI). Since 2004, overall incidence of candidemia has been almost stable around 1.4% among patients with hematological malignancies (HM)[1]. In 2015, Cornely et al reported an overall incidence of 0.42% among 27195 hematological patients admitted to hospital, which has grown up to 1.46% in HSCT recipients[2].

Reports of non-Candida fungemia are rare. In a multicenter study Nucci et al reported 11% of BSI due to *Fusarium spp* among 61 hematopoietic stem cell transplant recipients followed from 1985 through 2001[3].

Fungemia related death is a complex issue: the underlying malignancy itself play a paramount role in the development of IFI. The clinical suspicion and the prompt start of antifungal therapy may be the most effective intervention for improving patient outcomes in some cases.

We focused on epidemiology of fungal BSI in patients affected by either myeloid or lymphoid HM admitted over the past five years to 34 Italian hematology centers participating to the SEIFEM consortium.

MATERIALS AND METHODS

Study design

We retrospectively reviewed charts of hospitalized patients with HM in which a documented fungemia was diagnosed between January 2011 and December 2015 at 34 adult and pediatric Italian Hematology Departments. Demographic, hematological and microbiological data were registered in an electronic form. In particular, all participating centers collected information about age, sex, performance status according to ECOG scale, concomitant chronic diseases (chronic renal disease, diabetes mellitus, chronic obstructive pulmonary disease), previous surgical procedures, type of HM, last chemotherapy administration, type of transplantation, use and duration of steroids, absolute

neutrophil count and recovery of neutropenia, barrier damage following treatment (mucositis, parental nutrition), insertion and removal of central venous catheter (CVC), type of antifungal prophylaxis, presenting symptoms of fungemia (fever, gastro-intestinal or respiratory, septic shock) and parenchymal dissemination, antifungal treatment. The diagnostic work up of patients with fever was performed according to local clinical practice and similarly among the centers: rectal swabs at admission, blood culture at spiking fever, galactomannan assay twice weekly, chest X-ray at onset of fever, chest CT scan after 5-7 days of persistence of fever. According to clinical symptoms and laboratory findings, patients included in the study underwent additional radiological exams (brain and sinuses CT scan, abdominal ultrasound), bronchoalveolar lavage and fundus evaluation according to good clinical practice.

Outcome of patients was evaluated at 30 days from detection of fungemia, as the minimum follow-up available for all patients. Our research has been conducted following Helsinki declaration principles and approved by local ethical committee.

Definition

Fungemia was defined as at least one blood culture positive for a yeast or mold strain, associated to symptoms of infection referable to the fungal pathogens (i.e. fever, hypotension, respiratory distress, gastrointestinal symptoms). Breakthrough fungemia was defined by at least one positive blood culture

associated with above-mentioned symptoms occurring during systemic antifungal prophylaxis treatment started within 3 days[4]. Fungemia was considered as CVC-related if the isolated strain grew from CVC drawn blood faster than peripheral blood (with a differential time to positivity of 2 hours), or from a removed CVC-tip[5]. Severe neutropenia is defined as an absolute neutrophil count (ANC) less than 500 cells/mm^3. Recovery of neutropenia is defined as ANC stably over 1000 cells/mm^3. Bronchoscopy and biopsy proved lung and liver/spleen involvement.

Empirical antifungal therapy was defined as treatment started before microbiological identification of fungal isolate. Clinical efficacy of antifungal treatment was defined as complete resolution of clinical signs and symptoms of fungemia[2].

Survival was evaluated at 30 days from the microbiological isolation of fungi: death was attributed to infection, HM or other complication whenever possible. Fungi attributable mortality was defined as a death in patients with microbiological, histological, or clinical evidence of active fungal infection and no other clearly identifiable causes of death[6].

Statistical analysis

The aim of the study was to show clinical characteristics of patients and the prevalence of well-known risk factors associated to fungal disease in our population, identifying parameters predictive of outcome. Results are expressed

as means ± SD or medians (IQR) (continuous variables) or as percentages of the group from which they were derived (categorical variables). The Student t test and Mann-Whitney U test were used to compare normally and non-normally distributed continuous variables, respectively. Categorical variables were evaluated with the chi-square or two-tailed Fisher exact test. ORs and 95% CIs were calculated for all associations that emerged; a P value of <0.05 was considered significant. Multivariate logistic regression analysis was used to identify independent risk factors for 14-day mortality. Variables emerging from univariate analysis with P values of <0.1 were included in the multivariate model in a backward stepwise manner. All statistical analyses were performed with the Intercooled Stata program, version 11.

RESULTS

During the study period we recorded 215 fungal BSI among 199 adults and 16 pediatric patients with HM. Demographic and clinical characteristics according to the isolate species are reported in Table 1. A more detailed distribution of all isolated strains is showed in Table 2.

Isolated strains

Microbiological evaluation revealed that BSI was due to molds in 17 patients (8%) and yeasts in 198 patients (92%). Among 17 molds, 11 (65%) were *Fusarium spp*, 3 (17%) were *Aspergillus fumigatus*, and 1 for each of the remaining isolates *Mucor spp*, *Trichoderma viridae* and *Scedosporium apiospermium* (6%). *Candida spp* was identified in 174 patients (81%): *Candida albicans* accounted for 58 (33%) isolated strains, while the other *Candida* strains were distributed as follow: *C. tropicalis* 17 (10%), *C. glabrata* 24 (14%), *C. parapsilosis* 38 (22%), *C. krusei* 17 (10%), and other *Candida* 20 (11%). Among 24 other yeasts, 10 (42%) were *Geotrichum spp*, 6 (25%) were *Rhodotorula spp*, 4 (17%) were *Trichosporon spp*, 3 (12%) were *Saprochaeta spp*, and *Saccaromyces* was 1 (4%).

Epidemiological distribution

Molds BSI

Of the 17 patients with mold BSI, 13 were males (76%) and 13 (76%) were <60-year-old. Overall, the median age was 52 years (range 8- 75). Fifteen patients (88%) had a central venous catheter (CVC), 8 of which were centrally inserted. Positive blood cultures were detected from CVC in 5 (29%) and from peripheral blood in 12 patients (71%).

Use of parental nutrition and mucositis were present in 7 (41%) and 4 (23%) of patients respectively. Severe neutropenia was reported in 15 patients (88%), and only 2 (13%) recovered during antifungal treatment. Half of patients received steroids within 30 days before the onset of infections; none underwent previous surgical procedure. ECOG was ≥2 in 7 (41%) patients.

All but two patients received antifungal prophylaxis as following: 4 (27%) fluconazole and 11 (73%) mold active agents (posaconazole 6, itraconazole 3, voriconazole 2). All patients experienced fever, 2 had gastro-intestinal (GI) symptoms (12%); 5 (29%) respiratory symptoms and 3 (18%) septic shock. Organ dissemination (2 skin, 3 lung and 2 sinus) was documented in 6 patients. At the time of infection, 70% of patients had refractory or relapsed disease and 30% untreated disease.

Yeasts non-Candida BSI

In 24 patients BSI was due to a yeast other than Candida: they were almost equally distributed among female (54%) and male (46%), with a median age of 61 years (range 21-74 years). A CVC was present in 18 patients (75%), centrally inserted in 8 (33%): positive blood cultures were detected from CVC in 9 (37%), peripheral blood in 11 (46%) and both CVC and peripheral blood in 4 (17%) patients.

Use of parenteral nutrition and a previous surgical procedure were reported in 9 (37%) and 2 patients (8%) respectively. Moreover, mucositis was reported in 9 (37%) patients and 16 (67%) assumed steroids within 30 days before the onset of infection. Severe neutropenia was reported in 23 (96%) patients, only 5 of which (22%) recovered during antifungal treatment. ECOG was ≥2 in 9 (37%) patients.

Fourteen patients (58%) received antifungal prophylaxis: 3 (21%) with fluconazole and 11 (79%) with mold active agents. Symptoms of fungemia included fever in all patients, GI involvement in 7 (29%), respiratory symptoms in 2 (8%) and septic shock in 2 (8%). Organ dissemination occurred in 3 (12%) patients (1 skin, 1 lung and 1 liver). At the time of infection, underlying malignancy was active in 20 (87%) of patients: 11 (55%) had refractory or relapsed disease and 9 (45%) untreated disease. Four patients were in complete remission.

Candidemia

In 174 patients BSI was due to *Candida spp*: they were almost equally distributed among male (55%) and female (45%), with a median age of 56 years (range 40-66 years). Almost all patients had a CVC (168, 96%), centrally inserted in 99 (64%): positive blood cultures were detected from CVC in 69 (40%), peripheral blood in 61 (35%) and both CVC and peripheral blood in 44 (25%) patients.

Use of parental nutrition and a previous surgical procedure were present in 71 (41%) and 27 (15%) respectively. Moreover, mucositis was reported in 57 (33%) of patients, and 90 (52%) assumed steroids within 30 days before the onset of infections. Severe neutropenia was reported in 134 (77%) patients, 47 (35%) of which recovered during antifungal treatment. ECOG was ≥2 in 71 (41%) patients. Twenty-one patients (12%) suffered from chronic kidney disease and 6 (3%) from chronic obstructive pulmonary disease.

Eighty patients (46%) received antifungal prophylaxis: 36 (21%) with fluconazole and 44 (25%) with mold active agents. Fever was present in 171 (98%) patients, gastro-intestinal (GI) involvement in 56 (32%), respiratory symptoms in 43 (25%) and septic shock in 24 (14%). Organ dissemination (7 skin, 3 lung, 3 brain and 1 spleen) occurred in 12 patients (7%). At the time of infection, underlying malignancy was active in 139 (80%) patients: 76 (44%) refractory or relapsed disease, 63 (36%) untreated disease and 35 were in complete or partial remission of their HM.

Efficacy of treatment in patients with fungemia

Molds BSI

Among 17 patients, 2 (12%) did not receive antifungal treatment, and both deceased of infection before identification of isolate and CVC removal. Treatment was performed with echinocandins in 7 (46%) patients, followed by L-AmphB in 4 (27%) and various combination of two classes of antifungal agents in 4 (27%). Excluding untreated patients, we assessed an overall response rate of 33% (5

patients). CVC was removed after fungal isolation in 5 patients (33%): 3 deceased and 2 survived (both received a concomitant antifungal therapy).

Yeasts non-Candida BSI

Among 24 patients, 2 (8%) did not receive any antifungal treatment: identification of isolate succeeded death due to progression of HM in 1 patient and clinical improvement during mold active prophylaxis in another. Treatment was an echinocandin in 9 (41%) patients, followed by L-AmphB in 10 (45%) and other azoles in 3 (14%). Excluding untreated patients, we assessed an overall response rate of 50% (11 patients), even though a patient died of progression of its HM. CVC was removed after fungal isolation in 9 patients: 2 deceased and 7 survived under concomitant antifungal therapy.

Candidemia

Among 174 patients, 18 (10%) did not receive antifungal treatment: 12 (71%) deceased before identification of isolate, in 7 cases due to infection and in 5 cases due to progression of HM. In 5 out of 6 patients (29%) who survived despite absence of antifungal therapy, CVC was removed after fungal isolation: only 3 patients were receiving antifungal prophylaxis.

Among 156 patients, treatment was an echinocandin in 81 (52%) of patients, followed by L-AmphB in 39 (25%) and fluconazole in 23 (15%). Four patients (3%) were treated with various combination of two classes of antifungal agents

while in 9 (5%) other azoles were used. Excluding untreated patients, we assessed an overall response rate of 63% (99 patients); 6/66 (9%) patients died of either progression of their HM or other complications. CVC was removed after fungal isolation in 83 patients: 19 deceased and 64 survived.

Outcome of patients with fungemia

Considering all 215 patients, overall mortality at 30 days was 41%: when considering only death directly related to fungemia, mortality rate lowered to 21%. Progression of HM was reported as cause of death in 14%, and other causes were identified in 6% patients.

Mortality rate largely varied when considering the isolates responsible of BSI. Molds overall mortality rate was 70% (attributable mortality, AM 53%), while yeasts overall mortality rate was 39% (AM 18%). When distinguishing Candida and other yeasts, we found an overall mortality rate of 38% (AM 17%) and of 46% (AM 25%) respectively.

Predictors of mortality in patients with fungemia

At the univariate analysis, factors statistically associated with overall mortality were ECOG $\geq$2, use of steroids, chronic kidney impairment, GI and respiratory symptoms, signs of organ dissemination, septic shock and isolation of mold versus yeast, while recovery of neutropenia during therapy and removal of CVC were found to be protective (Table 3).

Sex, age, type and treatment of disease, occurrence of mucositis, diabetes, parenteral nutrition, chronic obstructive lung disease, previous fungal or bacterial infection, neutropenia at infection onset, duration of steroid therapy, insertion and type of CVC, type and duration of antifungal prophylaxis, fever, CVC related fungemia, isolation of Candida versus non-Candida strain were not statistically significant in univariate analysis.

In multivariate analysis, only ECOG $\geq$2, septic shock and removal of CVC retained their statistically significance for overall mortality (Table 4).

Predictors of mortality in the sub-group of patients with candidemia

At the univariate analysis, factors statistically associated with overall mortality in 174 patients with candidemia were ECOG $\geq$2, use of steroids, chronic kidney impairment, GI and respiratory symptoms, septic shock and concomitant bacterial sepsis, while isolation of *C.albicans* and removal of CVC were found to be protective (Table 3).

Sex, age, type and treatment of disease, occurrence of mucositis, diabetes, parenteral nutrition, chronic obstructive lung disease, previous fungal or bacterial infection, neutropenia at infection onset, duration and recovery of neutropenia during therapy, duration of steroid therapy, insertion and type of CVC, type and duration of antifungal prophylaxis, fever, signs of organ dissemination, CVC related candidemia were not statistically significant in univariate analysis.

In multivariate analysis, ECOG ≥2 and removal of CVC retained their statistically significance for overall mortality (Table 4).

DISCUSSION

Over the past 25 years, several reports have been published focusing on characteristics and outcome of candidemia in patients with HMs (Table 5). Until 1993, *C. albicans* was the main responsible of fungal BSI and fluconazole was consistently used as prophylaxis regimen. Since the broader use of mold active azoles, the epidemiology of Candida spp changed worldwide. A Northern America monocentric survey reported that 76% of yeast BSI were due to *C. non albicans* between 2001-2007 and up to 99% between 2008-2012 in a setting of antifungal prophylaxis with either mold active azoles or echinocandins and a high rate of breakthrough infection (72% and 94%, respectively) [7,8]. Lastly, a multicentric prospective survey recruiting patients in 13 centers among 8 countries between 2005-2009 reported 59% of *C. non albicans* in HM patients, with a breakthrough rate of 30%[2].

Less is known about other fungi BSI among patients with HMs. In 2004, Lionakis addressed for the first time the clinical value of mold isolation from peripheral blood in cancer patients. At least a 20% of mold isolations were defined true BSI among patients with HMs as compared to none in solid tumor patients[9]. In a survey of immunocompromised patients with *Scedosporium spp* infection, fungemia was reported in 33% of recipients of HSCT and 66% of patients with

HMs[10]. *Fusarium spp* was primarily detected in blood cultures in 28% of HSCT recipients with fusariosis[3] and was associated with poor outcome.

In our retrospective multicenter study, we identified 215 episodes of fungemia among 33 Italian tertiary care centers over a 6 year-surveillance. Unfortunately, neither data on the incidence of fungemia nor on the advantage of using a specific antifungal agent could be analyzed in the database. Similarly, data on empirical versus targeted therapy as well as on the timely removal of CVC are insufficient to draw any conclusion on the best approach. This survey provided useful information on the risk factors for fungemia and outcome on the basis of fungal isolation.

Despite this study enrolled few patients, some observations can be made. Unlike the patients with a yeast infection, those with a mold infection showed a delay in recovering from neutropenia and tended to have dissemination to skin, lung or sinuses. Moreover, most cases were breakthrough fungemias, occurred in two third of cases receiving a mold active prophylaxis: in particular, six patients received posaconazole prophylaxis in this group. As for antifungal therapy, almost half of patients were treated with echinocandins and about one third with a combination of two antifungal drugs. Accordingly to the data of literature, also in our population mold BSI was associated with a poor outcome with a 70% overall mortality at 30 days.

As previously reported[8,11], we found that more than 80% of fungal BSI were detected in patients with active hematologic disease (refractory/relapsed or newly diagnosed HM): the underlying malignancy itself play a paramount role in

the development of IFI. Moreover, despite the median age of our population was not elevated, an ECOG performance status >2 was detected in 40% of patients. At univariate analysis, performance status >2, use of steroids, renal impairment, organ dissemination, signs of GI and respiratory failure, septic shock with multiorgan failure and isolation of molds were statistically associated to increased overall mortality. On the contrary, removal of CVC and recovery of neutropenia were protective factors for survival. In multivariate analysis, worse performance status, septic shock and removal of CVC emerged as prognostic factors for overall mortality. Unexpectedly, both overall and attributable mortality were not influenced by neutropenia itself rather than recovery of neutropenia, as the restored killing activity of granulocyte is of paramount importance against fungi infections. Removing CVC was helpful for the management of fungemia, even though a clear advantage of early versus late removal was not observed. Organ involvement and multiorgan failure syndrome are associated with fast worsening of clinical condition and dismal prognosis. Although antifungal prophylaxis has changed the epidemiology of fungal infections by reducing incidence of IFI, particularly mold infections, prophylaxis administration had no impact on survival, and none of antifungal drugs could demonstrate a superiority in respect of overall mortality. Hematological malignancy itself is the major risk for mortality: the rates of response to treatments widely vary according to the diseases. Moreover, in the registrative study of posaconazole in comparison with other azoles in the setting of prophylaxis of IFI during chemotherapy for AML and MDS, the authors

considered incidence of proven or probable IFI instead of mortality as primary end point. Indeed, starting antifungal therapy as soon as a fungal infection is suspected in high risk patient presenting with septic shock is strongly recommended as survival can be improved if fungemia is confirmed. A de-escalation approach is always possible if a fungemia is not confirmed.

C. albicans accounted for 34% of all Candida strains with no statistically significant differences among the centers. This is in line with other reports[2,7,8,12,13] and it is probably a consequence of the use of antifungal prophylaxis, especially in patients with acute myeloid leukemia (AML) where *Candida spp* BSI are more frequently detected. As compared with the SEIFEM studies performed between 1999 and 2003, a statistically significant reduction in the incidence of candidemia was found (p= <0.0001, CI 1.41-1.73), particularly among patients with AML (from 4.1% to 1.5%, p= <0.001, CI 1.46-1.82). This was probably due to a wider use of posaconazole for antifungal prophylaxis in AML patients undergoing induction chemotherapy [14].

Candidemia is associated usually with a good outcome due to the efficacy of the antifungal agents in managing *Candida* BSI compared to other yeasts and molds. Tending to confirm a decreasing mortality rates over the last years, our retrospective study showed a 38% overall and 17% attributable mortality at 30 days (Table 5).

In conclusion, fungemia remains a notable problem, due the high mortality rate, in hematological malignancies. A correct knowledge of epidemiology and of those parameters that can influence the outcome of this complication could be

extremely useful for a better personalized approach tailored to the needs and characteristics of each single patient.

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ACKNOWLEDGMENTS

All authors contributed to recruitment of patients. MT did statistical analyses; MC and LP wrote the manuscript; FM, CC, AC, AN, FA and AB reviewed the manuscript.

CONFLICT OF INTERESTS

The authors have no conflict of interest.

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Table 1. Characteristics of 215 patients with Fungemia

	Molds (17)	Candida spp (174)	Other Yeasts (24)
Sex			
Male	13 (76)	95 (55)	11 (46)
Female	4 (24)	79 (45)	13 (54)
Age (median)	52 (8-75)	56 (40-66)	61 (21-74)
• </=60	13 (76)	102 (59)	12 (50)
• >60	4 (24)	72 (41)	12 (50)
Haematological disease			
• AML	8 (47)	73 (42)	15 (63)
• ALL	4 (24)	21 (12)	0
• NHL	1 (6)	51 (29)	5 (21)
• HL	0	3 (2)	0
• CML	3 (17)	1 (1)	1 (4)
• MM	0	13 (7)	1 (4)
• CLL	0	4 (2)	1 (4)
• MDS	1 (6)	8 (5)	1 (4)
Hsct (Yes/No)	1/16 (6)	55/119 (32)	3/21 (12)
• Autologous	0	19 (35)	0
• Allogeneic	1 (6)	36 (65)	3 (12)
Phase of disease			
• Onset	5 (30)	63 (36)	9 (37)
• CR	0	25 (14)	4 (17)
• PR	0	10 (6)	0
• Resistance	3 (17)	38 (22)	5 (21)
• Recurrence	9 (53)	38 (22)	6 (25)
Central venous catheter	15 (88)	168 (96)	18 (75)
• PICC	7 (47)	56 (36)	10 (55)
• Central	8 (53)	99 (64)	8 (45)
ECOG ≥2	7 (41)	71 (41)	9 (37)
Risk Factors			
• Parenteral nutrition	7 (41)	71 (41)	9 (37)
• Mucositis	4 (24)	57 (33)	9 (37)
• Surgical procedures	0	27 (15)	2 (8)
• Diabetes	4 (24)	18 (10)	3 (12)
• CKD	1 (6)	21 (12)	2 (8)
• COPD	2 (12)	6 (3)	0
Organ involvement	6 (35)	12 (7)	3 (12)
• Skin	2 (34)	7 (58)	1 (33)
• Lung	3 (50)	3 (25)	1 (33)
• Brain	0	3 (25)	0
• Sinuses	2 (34)	0	0
• Liver/Spleen	0	1 (8)	1 (33)
Neutropenia	15 (88)	134 (77)	23 (96)

Recovery of neutropenia	2 (13)	47 (35)	5 (22)
Steroids	9 (50)	90 (52)	16 (67)
Clinical features			
• Fever	17 (100)	171 (98)	24 (100)
• GI symptoms	2 (12)	56 (32)	7 (29)
• Respiratory symptoms	5 (29)	43 (25)	2 (8)
• Shock	3 (18)	24 (14)	2 (8)
Antifungal Prophylaxis	15 (88)	80 (46)	14 (58)
• Fluconazole	4 (27)	36 (45)	3 (21)
• Mold active	11 (73)	44 (55)	11 (79)
Therapy	15 (88)	157 (90)	22 (92)
• Ambisome	4 (27)	39 (25)	10 (45)
• Echinocandins	7 (46)	81 (52)	9 (41)
• Fluconazole	0	23 (15)	0
• Other azoles	0	9 (5)	3 (14)
• Combination therapy	4 (27)	4 (3)	0
Efficacy of therapy	5 (33)	99 (63)	11 (50)
Evolution			
Death	12 (70)	66 (38)	11 (46)
Cause of death			
• Infection	9 (53)	30 (17)	6 (25)
• Haematological disease	3 (17)	21 (13)	5 (21)
• Other	0	15 (8)	0

Table 2. Distribution of all isolated strains

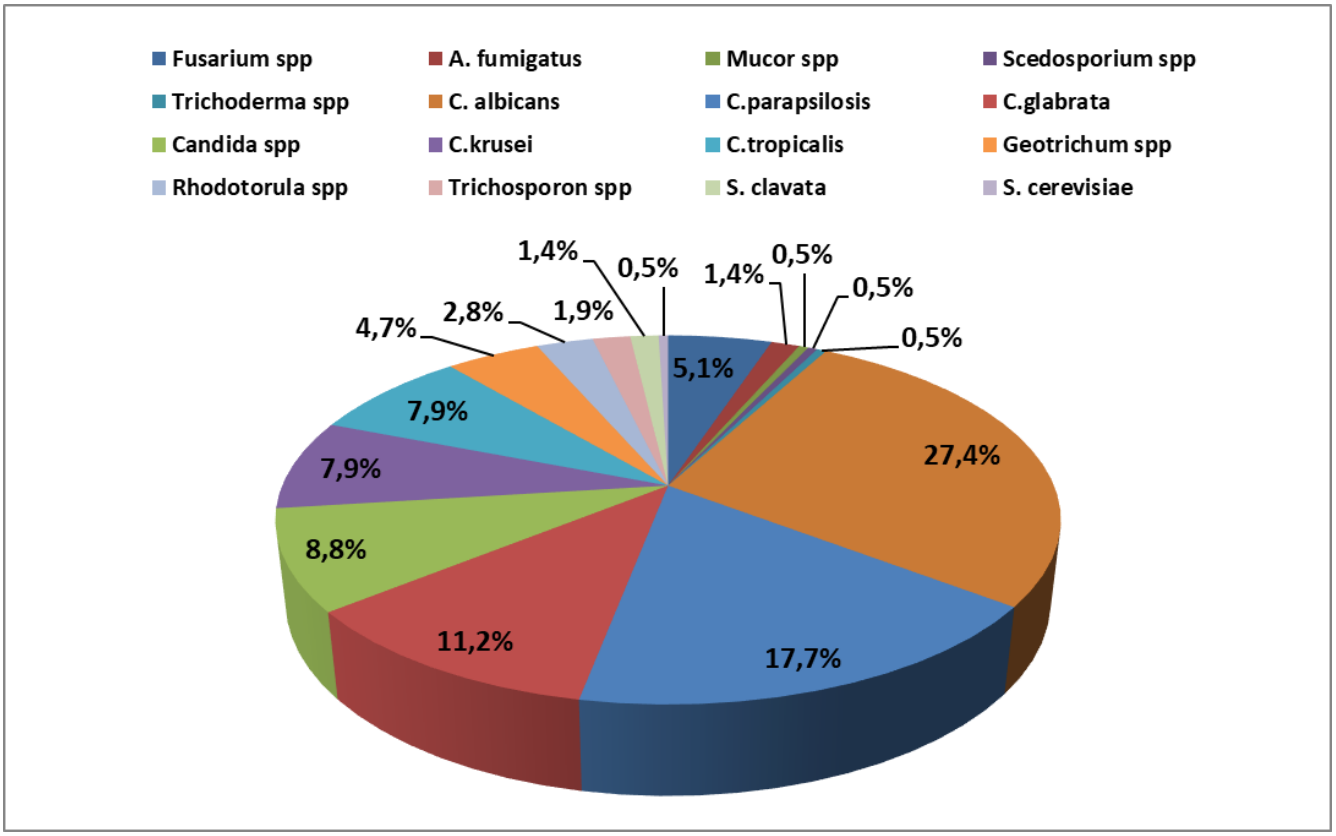

Table 3. Univariate analysis for overall mortality

	ALL FUNGEMIE		CANDIDEMIA	
	Odd's ratio	**p-value**	**Odd's ratio**	**p-value**
Performance Status >2	4.75 (2.53-8.91)	0.00001	5.34 (2.61 -10.97)	0.00001
Chronic kidney disease	2.63 (1.01-7.17)	0.00259	2.44 (0.87-6.98)	0.0530
Steroid administration	2.11 (1.16-3.85)	0.0080	1.97 (1.01-3.88)	0.0319
GI symptoms	1.89 (1.00-3.56)	0.00325	1.88 (0.93-3.79)	0.0541
Respiratory symptoms	3.77 (1.84-7.85)	0.0001	4.56 (2.07-10.21)	0.00001
Septic shock	4.55 (1.80-12.47)	0.0003	4 (1.48-11.47)	0.0018
Multiorgan failure	2.63 (1.01-7.17)	0.00259		
Molds Vs Yeasts	3.77 (1.17-14.12)	0.0109		
Concurrent bacterial sepsis			2.19 (0.89-5.41)	0.0562
CVC removal	0.27 (0.14-0.53)	0.00001	0.27 (0.13- 0.56)	0.0001
Neutrophil recovery	2.38 (1.30-4.35)	0.0023		
C. albicans vs. non-albicans			0.25 (0.12-0.51)	0.0001

Table 4. Multivariate analysis for overall mortality

	ALL FUNGEMIE		**CANDIDEMIA**	
	Odd's ratio	**p-value**	**Odd's ratio**	**p-value**
Performance Status >2	4.33 (2.24- 8.37)	0.00001	4.29 (2.06- 8.91)	0.00001
Shock	2.71 (1.16-3.85)	0.042		
CVC removal	0.41 (0.21-0.80)	0.010	0.39 (0.18-0.81)	0.013

Table 5. Studies on candidemia in patients with HMs over the last 30 years

	Period of observation	Number of patients	Incidence	Breakthrough rate	Candida non albicans isolates	Overall mortality (30 days)	Attributable mortality (30 days)
Pagano Eur J Hematol 1999	1988-1997	76	_	86%	70%	49%	26%
Viscoli CID 1999	1992-1994	150	_	40%	64%	39%	24%
Pagano Haematologica 2006	1999-2003	175	1.5	_	57%	_	33%
Sipsas Cancer 2009	2001-2007	170	_	72%	76%	68%	19%
Horn Clin Inf Dis 2009	2004-2008	2019 (all cause hospitalization)	_	43%	54.4%	35.2% at 12 weeks	_
Zirkel Med Mycol 2012	2003-2009	21 (14 HM)	1.4/1000 hospitalization	25%	72%	56%	_
Chen Int J Antimicrob Agents 2012	2001-2010	111	4.3%	_	68.4%	31.5%	_
Bergamasco Mycoses 2013	2003-2007	117	_	46%	69%	54%	
Cornely CID 2015	2005-2009	140 (HM and cancer)	0.19%	32.8%	59%	35%	72% at 2 weeks
Gedik Therapeutics and Clinical Risk Management 2014	2010-2012	18	_	_	_	16.6%	_
Gamaletsou Clin Microb Inf 2014	2009-2012	40	1.4/1000	53%	87,50%	45%	27,50%
Dewan Hem Onc Stem Cell 2015	2010-2012	150 (both adults and pediatrics)	_	_	73.3%	_	_
Puig-Asensio Clin Microb Inf 2015	2010-2011	43	_	46.5%	71.1%	30.2%	_
Wang J Antimicrob Chemother 2015	2008-2012	65	_	94%	99%	52%	_
Lortholary Intensive Care Med 2017	2002-2014	586	_	20.6%	51.5%	35.6%	_
Present study	2011-2015	174	_	46%	66.6%	38%	17%