Presentation Number
M-312
Fungal Epidemiology

Increase of Candidemia due to non- albicans Candida Species in Oncohematological (OH) Patients.

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on behalf of CANDIPOP Project, GEIH-GEMICOMED (SEIMC) and REIPI, Spain.

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ABSTRACT

Background: We aimed to describe the distribution of *Candida* species, antifungal susceptibility and outcome in patients with hematological (HM) and oncological (O) malignancies in Spain looking for differences between these two groups. **Methods:** A prospective multicenter population-based surveillance program on *Candida* BSI was implemented in 29 hospitals from 5 areas in Spain (population 7,237,228) from May 2010 to April 2011. Case was defined as the first positive blood culture of *Candida* in a surveillance area resident. We analyzed crude mortality rate (within 30 days) and early mortality (3-7 days). **Results:** Among 752 candidemia episodes, 283 (39%) were detected in OH (225 and 58 respectively); 48 (17%) episodes were breakthrough candidemias. Risk factors were: 35% previous immunosuppressive therapy (23.7% chemotherapy), 11.3% neutropenia and 9.5% mucositis. 79.9% cases had central venous catheter (32.3% long-term) and 61 (21.6%) patients had received a prior azole therapy. Candidemia was catheter-related in 37% in both HM and O patients. *C.albicans* was the most common isolate (42%), followed by *C.parapsilosis* (22%), *C.glabrata* (15%), *C.tropicalis* (10%), *C.guilliermondii* (3%), *C.krusei* (3%) and others (5%). In HM patients non-*C.albicans* species were more frequent (77% vs 53%, p< 0.000) and, particularly, *C.tropicalis* and *C.guilliermondii* were more likely to occur (20% vs 7.5 %, and 8.3% vs 1.7%, respectively). Azole prophylaxis was a risk factor for *C.krusei* candidemia. Overall rate of decreased susceptibility to fluconazole (MIC≥4) was higher in OH patients (17% vs 13.5%, p=0.16). The mortality rate was 30.7 % within 30 days (13.4% within 7 days) without any differences between HM and O patients. Multivariate analysis showed that early catheter removal was a protective factor for early mortality in non-neutropenic patients whose source of infection was either primary or catheter-related (OR 0.19; 95% CI, 0.044 to 0.83). **Conclusions:** Non-*albicans* *Candida* species are emerging as the predominant isolates especially in hematological patients. Early catheter removal is recommended for preventing early mortality.

INTRODUCTION

Invasive fungal infections, including candidemia, pose a major threat to patients with impaired immune defenses. These patients are subjected to more aggressive management of their underlying malignancies with chemotherapeutic agents and transplantation, which lead to more profound neutropenia and damage of the mucosal integrity.

Although *Candida albicans* remains the most common fungal isolate obtained from the blood of patients with invasive fungal infection, several studies have demonstrated a trend toward an increased prevalence of infections with *non-albicans Candida* spp., such as *C. glabrata* and *C. krusei*.

Moreover, some differences have been described in the epidemiology of candidemia between O and HM patients due to the extended use of fluconazole in the last group.

Candidemia not only is associated with increased mortality and morbidity rates but also prolongs hospitalization and increases medical care costs

OBJECTIVE

- To describe the distribution and antifungal susceptibility of *Candida* species in patients with hematological (HM) and oncological (O) malignancies in Spain.
- To look for differences between HM and O patients.
- To know the outcome of Candida fungemia in these population.
- To analyze the mortality directly attributable to the infection.

MATERIAL AND METHODS

DEFINITIONS

Incident case of candidemia: The first positive blood culture of *Candida* spp obtained from a peripheral vein.
New cases : isolation of different *Candida* species or candidemias occurring > 30 days after previous episode

DATA COLLECTION

- Reporting of cases was laboratory-based.
- Standardized case-report form was used.
- Audits to local laboratories were performed.
- Written patient consent was obtained for all participants.

OUTCOMES

- Patients were followed for 30 days.
- Overall mortality rate at 30 days.
- Analysis of risk factors for early (3-7) mortality by multivariable logistic analysis.

MICROBIOLOGICAL METHODS

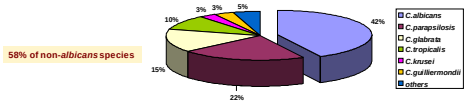
- Species confirmation and antifungal susceptibility testing was performed at the **National Center for Micology**, Madrid, Spain

- **EUCAST MIC breakpoints** were used for susceptibility interpretation of fluconazole:
  - Susceptible: ≤ 2 µg/ml.
  - Susceptible dose-dependent: 4 µg/ml
  - Resistant: > 4 µg/ml

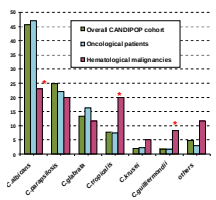
RESULTS

•Among 752 candidemia episodes, 283 (39%) were detected in OH (225 and 58 respectively).

Figure 1. *Candida* species distribution

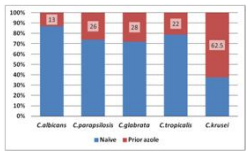


• Differences between oncological (O) and hematological (HM) patients



*statistically significant differences

• *Candida* species according to previous azole exposure



Azole prophylaxis was a risk factor for *C.krusei* candidemia [OR 3.05, 95% CI, 1.69-5.47]

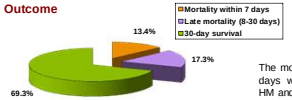
Table 1. Demographic characteristics and clinical data of study population

Characteristics*	Total, N= 283	Oncological patients, N=225	Hematological malignancy, N=58	P value
Male	175 (61.8)	144 (64)	31 (53.4)	NS **
Median age (years)	66	68	55	<0.001
Source of infection				
Primary Definite catheter-related	150 (53) 105 (37)	115 (51) 83 (37)	36 (62) 21 (36.2)	NS NS
Co-morbidities				
Diabetes Cardiovascular disease	60 (21.1) 65 (23)	55 (24.4) 61 (27.1)	5 (8.6) 4 (7)	0.007 < 0.001
COPD	38 (13.4)	34 (15.1)	4 (6.8)	NS
HIV infection	7 (2.5)	3 (1.3)	4 (6.9)	0.036
In ICU at diagnosis	47 (18.8)	37 (16.5)	10 (17.2)	NS

Risk Factors *	Total, N= 283	Oncological patients, N=225	Hematological malignancy, N=58	P value
Prior antibiotic therapy	269 (95.1)	213 (94.7)	56 (96.6)	NS **
Prior antifungal therapy azole exposure	70 (24.7) 61 (21.6)	40 (17.8) 36 (16)	30 (51.7) 25 (43)	< 0.001
Central venous catheter (CVC) Long-term CVC	226 (79.9) 73/226 (32.3)	175 (78.1) 44/175 (25.1)	51 (87.9) 29/51 (56.8)	NS < 0.001
Surgery in previous 3 months	163 (57.6)	155 (68.9)	7 (12.1)	< 0.001
Total parenteral nutrition	142 (50.1)	121 (53.9)	21 (36.2)	0.017
Prior *Candida* colonization	91 (32.2)	80 (30.5)	11 (19)	0.022
Prior immunosupressive medication Cytotoxic chemotherapy	99 (35) 67 (23.7)	57 (25.3) 38 (17)	42 (72.4) 29 (50)	< 0.001
Neutropenia < 1x10⁹/L[a] < 0.5 x10⁹/L <0.1x x10⁹/L	32 (11.3) 7 (2.5) 22 (7.8)	5 (2.2) 1 (0.4) 3 (1.3)	27 (46.6) 6 (10.3) 19 (32.8)	< 0.001
Breakthrough candidemia [b]	48 (17)	23 (10.3)	25 (43.1)	< 0.001
Isolates with decreased susceptibility to fluconazole (MIC ≥ 4 mg/L)	49/288 (17)	30/227 (13.2)	19/61 (31)	< 0.001

Variables were determined within the preceding month, otherwise indicated
* All data are given as n (%). ** NS: Not statistically significant
[a] at candidemia diagnosis
[b] receiving > 3 days of antifungal treatment prior to candidemia

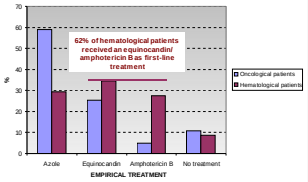
Outcome



The mortality rate was 30.7 % within 30 days without any differences between HM and O patients.

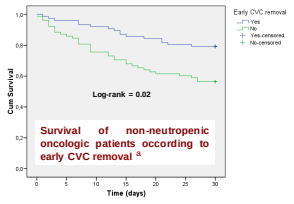
Therapeutic mesures

1.- EMPIRICAL TREATMENT



2.- CENTRAL VENOUS CATHETER (CVC) REMOVAL

CVC removed within 48 hours
- 82/175 (46.8%) in O patients
vs
- 15/51(29.4%) in HM patients
(p=0.015)



[a] subanalysis of patients whose source infection was primary or catheter-related

Table 2. Predictors of early mortality (3-7 days) in non-neutropenic adult patients

Variable	Univariate analysis OR (95% CI)	P value	Multivariate analysis OR (95% CI)	P value
High-severity of illness[a]	4.9 (2.08-11.5)	< 0.001		
COPD	3.2 (1.36-7.6)	0.003	4.9 (1.16-20.9)	0.03
Pitt score ≥ 2	3.5 (1.38-8.9)	0.005		
Catheter removal within 48 h[b]	0.27 (0.08-0.94)	0.047	0.19 (0.044-0.83)	0.027

[a] APACHE > 20 for patients admitted to Intensive Care Unit (ICU) and Charlson ≥ 5 for adults outside ICU.
[b] Patients with central venous catheter with primary/catheter-related source of infection (n= 164)

DISCUSSION

•Risk factors for candidemia showed a different pattern between oncological and hematological patients. Hematological patients were more likely to have received chemotherapy previously, been exposed to prior antifungal drugs and to be neutropenic in comparison to oncological patients.

•Overall, 48 (17%) episodes were breakthrough candidemias in patients receiving antifungal prophylaxis or empirical treatment.

•79.9% of our patients had central venous catheter and fungemia related to them was recorded in 37% in both HM and O patients, without differences between the groups.

•Although *C.albicans* was the most common isolate (42%), in HM patients non-*C.albicans* species were more frequent (77% vs 53%, p< 0.000) and, particularly, *C.tropicalis* and *C,guilliermondii* were more likely to occur (20% vs 7 %, and 8.3% vs 1.7%, respectively) as has been described in other series.

•Azole prophylaxis was a risk factor for *C.krusei* candidemia as happens in other studies.

•Overall rate of decreased susceptibility to fluconazole (MIC≥4) was higher in OH patients (17% vs 13.5%, p=0.16).

•The mortality rate was 30.7 % within 30 days (13.4% within 7 days) without any differences between HM and O patients and equal than mortality recorded in global CANDIPOP population

•Univariate analysis showed that the subgroup of non-neutropenic patients may benefit from early catheter removal. In multivariate analysis, and after adjustment for severity of illness, this therapeutic measure was a protective factor for early mortality (OR 0.19; 95% CI, 0.044 to 0.83).

CONCLUSIONS

1.- Non albicans-Candida species are emerging as predominant isolates specially in hematological patients.

2.- Early catheter removal could be benefitial for preventing early mortality in non-neutropenic patients with primary or CVC-related candidemia.

This study was supported by researchgrants from Gilead Spain, MSD Spain, Astra Zeneca Spain, and Pfizer Spain.