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Clinical presentation of candidaemia in elderly patients: experience in a single institution

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ABSTRACT

Objective. To analyse the clinical presentation of candidaemia in elderly patients.

Methods. A comparison of clinical presentation of candidaemia cases was carried out in a Spanish tertiary hospital between January 2010 and September 2015.

Results. Forty-five cases (32%) corresponded to elderly patients (≥ 75 years) and 95 cases (68%) to non-elderly patients (16-74 years). A higher proportion of elderly patients presented solid tumour (51% versus 32%, $p=0.026$) and a lower proportion had undergone solid or hematopoietic transplantation (0% versus 28%, $p<0.001$). Fewer elderly patients (16 patients, 36%) had a central venous line inserted than non-elderly patients (81 patients, 85%, $p<0.001$). Isolation of *Candida parapsilosis* was significantly lower among elderly (13.3%) than among non-elderly patients (32%, $p=0.015$). Fundoscopy was carried out in 20 elderly (44%) and in 64 younger patients (67%, $p=0.009$). The proportion of patients who underwent echocardiography was similar in both groups (56% vs 66%, respectively; $p=0.218$). Adequate antifungal treatment within the first 48 hours was administered in 16 elderly patients (36%) and 58 younger patients (61%, $p=0.005$). Catheter removal was carried out in 9 elderly patients (68.1%) and in 40 non-elderly patients (49%, $p=0.544$). Mortality was higher among elderly patients (55.6%) than non-elderly patients (36.8%; $p=0.037$).

Conclusions. Elderly patients account for a substantial proportion of patients suffering from candidaemia in recent years. The clinical management of these patients was less appropriate than in younger patients with respect to fundus

examination and the prescription of appropriate antifungal treatment. Mortality in elderly patients was higher than in younger patients.

Keywords: Candidaemia; Mortality; Aged; Antifungal Agents; Central Venous Catheters

Presentación clínica de candidemia en pacientes ancianos: experiencia de un hospital

RESUMEN

Objetivo. Analizar la presentación clínica de candidemia en pacientes ancianos.

Métodos. Se realizó una comparación de la presentación clínica de los casos de candidemia en un hospital terciario español entre enero de 2010 y septiembre de 2015.

Resultados. Cuarenta y cinco casos (32%) correspondieron a pacientes ancianos (≥ 75 años) y 95 casos (68%) a pacientes no ancianos (16-74 años). Un número menor de pacientes ancianos (16 pacientes, 36%) portaban un catéter central en comparación con los pacientes más jóvenes (81 pacientes, 85%, $p<0,001$). El aislamiento de *Candida parapsilosis* fue significativamente menor entre los ancianos (13,3%) que entre los más jóvenes (32%, $p = 0,015$). Se realizó exploración del fondo de ojo en 20 ancianos (44%) y en 64 pacientes más jóvenes (67%, $p = 0,009$). La proporción de pacientes que se sometieron a ecocardiografía fue similar (56% vs 66%, respectivamente, $p = 0,218$). Se administró tratamiento antimicótico adecuado en las primeras 48 horas en 16 pacientes ancianos (36%) y 58 pacientes más jóvenes (61%, $p = 0,005$). La retirada del catéter central se realizó en 9 pacientes ancianos (68,1%) y en 40 pacientes no ancianos (49%, $p = 0,544$). La mortalidad fue mayor entre los pacientes ancianos (55,6%) que los no ancianos (36,8%, $p = 0,037$).

Conclusiones. Los pacientes ancianos representan una proporción sustancial de pacientes que padecen candidemia.

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El manejo clínico de estos pacientes fue menos apropiado que en pacientes más jóvenes. La mortalidad en pacientes ancianos fue mayor que en pacientes más jóvenes.

Palabras clave: candidemia; mortalidad; ancianos; antifúngicos; catéter venoso central

INTRODUCTION

Invasive fungal infections are characterized by their increasing incidence and high mortality¹. Candidaemia represents an important invasive fungal infection, particularly among critically ill patients². Elderly patients also constitute a group that commonly suffers from candidaemia, which has been related to a high rate of chronic conditions, such as diabetes mellitus, immunosuppressive therapy and frequent oropharyngeal colonization with *Candida*^{3,4}. Certain measures as restricting parenteral nutrition, prompting earlier enteral feeding, and reducing use of antibiotics have been promoted to reduce the incidence of candidaemia in these patients^{5,6}.

Episodes of candidaemia in patients with advanced age present several peculiar characteristics, the most important being high mortality^{7,8}. Failure to receive adequate antifungal therapy or catheter removal are a common risk factor for death in candidemic patients⁶. Therefore, a better understanding of some aspects related to clinical presentation and therapeutic approach may be decisive for better management of candidaemia in patient with advanced age^{5,6}.

We decided to analyse the clinical presentation and management of candidaemia in elderly patients.

MATERIALS AND METHODS

Setting, patients and study design. The study, focused on candidaemia in elderly patients, was carried out at a single institution in Spain, a 620-bed tertiary teaching hospital at Madrid (Spain) that is reference in organ solid transplant. Between January 2010 and September 2015, *Candida* spp. positive blood cultures were identified in the microbiology laboratory of the participating hospital. The blood culture bottles were incubated in automated incubator systems (BACTEC 9240 and Bactec FX BD). Definitive identification and sensibility was confirmed in every case using techniques of molecular biology in a reference centre of Spain (Instituto de Salud Carlos III). Anti-fungal susceptibility was tested by E-Test (2010-2011) and Sensititre Yeast One® (2012-2015). Susceptibility criteria by all strains were defined using EUCAST species-specific breakpoints (Clinical breakpoints - fungi v7.0).

Given the observational nature of the research, patients were managed according to routine clinical care. The ethics committees of the participating institution approved the study, and written consent was obtained from all patients. Patients were divided into two groups: elderly patients (≥ 75 years) and younger patients (16-74 years)

Definitions. Definitions have been described in a previous publication⁴. In brief, an incident case was the first pos-

itive *Candida* spp. blood culture. Outpatient-acquired cases were candidaemias detected ≤ 2 days after hospitalization. In the case of a patient presenting more than one episode of candidaemia, all episodes were considered in the analysis. The Charlson index was used to represent comorbidity in adults⁹. Sepsis, severe sepsis or septic shock were recorded on the day of candidaemia¹⁰. Timing to central venous catheter (CVC) removal and to antifungal administration was the interval between incident blood culture and implementation of these measures. Adequate antifungal treatment was classified as use of the correct dose of antifungal agent for a susceptible *Candida* isolate. Mortality recorded during admission in which candidaemia was detected.

Microbiological studies. *Candida* isolates corresponding to episodes recorded were processed and stored at hospital as described elsewhere¹¹. Susceptibility to antifungal drugs and interpretation of resistance rates were investigated according to the protocols¹² and clinical breakpoints of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [http://www.eucast.org/clinical_breakpoints/]¹³.

Data analysis. Quantitative variables were reported as median and interquartile range (IQR), and categorical variables as counts (%). Episodes of candidaemia in all patients (excluding those younger than 16 years) were included in the study. The chi-square test or Fisher exact test was used to compare the distribution of categorical variables, and the Student t-test or Mann-Whitney U test for quantitative variables. Significance was set at a p value of less than 0.05.

RESULTS

In total, 140 episodes occurred in 45 elderly patients (≥ 75 years) and in 90 non-elderly patients (16-74 years). Two patients presented three episodes of candidaemia and one patient two episodes during the study period, all of them in non-elderly patient group. There was a predominance of female gender and more cases in patients residing in nursing homes among the elderly patients with candidaemia.

There were more patients suffering from solid neoplasm among elderly patients, and less with hematologic neoplasm, human immunodeficiency virus (HIV) infection or transplantation than among younger patients (table 1). Other risk factors, such as central venous catheter, parenteral nutrition or immunosuppressive therapy, were less common in elderly patients. There was no relevant difference regarding previous abdominal surgery. In relation to the source of infection, there were fewer cases of elderly patients bearing central catheter. Ocular involvement occurred only in the non-elderly group (7.4%, $p=0.061$). Endocarditis was confirmed in 2 cases (8%) among elderly patients versus 2 cases (3.2%) among younger patients ($p=0.218$).

The distribution of *Candida* species differed between elderly and younger patients. Although there was a comparable rate of infections caused by species other than *C. albicans*, there were more cases due to *C. parapsilopsis* among non-el-

Table 1		Clinical characteristics of study population and clinical data of candidaemia episodes according to patient age		
	Elderly patients ^a (n=45)	Non-elderly patients (n=95)	RR (CI 95%)	P
Age, years, median (IQR)	62 (54-70)	83 (79-87)		<0.001
Male gender	19 (42.2)	60 (63.2)	0.67 (0-46-0.97)	0.020
Community acquired	5 (11.1)	10 (10.5)		0.916
Nursing home	20 (44.4)	5 (5.3)	8.44 (3.39-21.05)	<0.001
Previous trimester admission	18 (40)	31 (32.6)		0.393
Diabetes mellitus	13 (28.9)	18 (18.9)		0.185
HIV	0	2 (2.1)		0.326
Solid neoplasm	23 (51.1)	30 (31.6)	1.62 (1.07-2.44)	0.026
Hematologic neoplasm	3 (6.7)	18 (18.9)		0.058
Solid-organ transplantation	0	9 (9.5)		0.032
HSCT	0	8 (8.4)		0.045
Corticosteroids ^b	6 (13.3)	17 (17.9)		0.498
Immunosuppressive therapy	2 (4.4)	18 (18.9)	0.23 (0.06-0.97)	0.022
CVC	16 (35.6)	81 (85.2)	0.42 (0.28-0.62)	<0.001
Abdominal surgery	12 (26.7)	30 (31.6)		0.553
Mechanical ventilation	4 (8.8)	23 (24.2)	0.37 (0.13-1.00)	0.032
Total parenteral nutrition	12 (26.7)	51 (53.7)	0.50 (0.30-0.83)	0.003
Ecocardiography	25 (55.6)	63 (66.3)		0.218
Endocarditis	2 (8)	2 (3.2)		0.327
Fundoscopy	20 (44.4)	64 (66.6)	0.46 (0.31-0.67)	0.009
Chorioretinitis	0	7 (7.4)		0.061
Severe sepsis or shock	25 (55.6)	49 (51.6)		0.660
Previous antifungal drug ^c	11 (24.4)	21 (22.1)		0.759
Previous echinocandins ^c	0	10 (10.5)		0.030
Previous fluconazole ^c	7 (15.6)	14 (14.7)		0.899
Previous antibiotic ^c	41 (91.1)	87 (92.6)		0.768
<i>Candida</i> species ^d	46	97		
<i>C. albicans</i>	25 (54.3)	45 (46.4)		0.376
<i>C. parapsilosis</i>	6 (13.3)	31 (32.6)	0.41 (0.18-0.91)	0.015
<i>C. glabrata</i>	9 (19.6)	11 (11.3)		0.187
<i>C. tropicalis</i>	4 (8.7)	3 (3.1)		0.148
<i>C. krusei</i>	0	2 (2.1)		0.328
Other	2 (4.3)	5 (5.2)		0.835
Fluconazole non-susceptibility ^e	10 (21.7)	21 (21.6)		0.987
Echinocandin non-susceptibility ^e	3 (6.5)	14 (14.4)		0.173
CVC removal, first 48 h ^f	9 (56.2)	40 (49.3)		0.617
Adequate treatment, first 48 h	16 (35.6)	58 (61.1)	0.58 (0.38-0.89)	0.005
In-patient mortality	25 (55.6)	35 (36.8)	1.51 (1.04-2.19)	0.037

^aElderly patients, ≥ 75 years. Non-elderly patients, < 75 years. Two elderly patients presented three episodes of candidaemia and one patient two episodes during the study period, all of them in non-elderly patient group. ^bEquivalent prednisone dose > 20 mg/day. ^cDuring the previous month, several patients received more than one antimicrobial drug. ^dOne patient ≥ 75 years and two patients < 75 years presented mixed candidaemia. ^eIncludes resistant strains and with intermediate sensitivity. ^fPercentage of catheter removal during first 48 hours considering patients having CVC.

IQR: Interquartile range, HSCT: hematopoietic stem cell transplantation, HIV: Human immunodeficiency virus infection. CVC: central venous catheter.

derly patients. The proportion of episodes due to *C. albicans* in the elderly patients living in a nursing home was 65% (13 episodes isolates) and 46.3% (57 episodes, $p=0.151$) in all other patients. Eleven episodes of candidaemia in the elderly group (24.4%) had been preceded by antifungal treatment during the previous month. Previous echinocandin prescription was only noted in non-elderly patients (10.5%, $p=0.030$).

Thirty-eight elderly patients received antifungal therapy for candidaemia episode (82.2%) compared to 87 cases (91.6%) among the younger group ($p=0.204$). The antifungal drugs used in younger patients were fluconazole 70 cases (73.7%), echinocandins 45 cases (47.4%), amphotericin B 16 cases (16.8%), voriconazole 10 cases (10.5%) and posaconazole 1 case (1.1). The antifungal drugs used in elderly patients were fluconazole 29 cases (64.4%), echinocandins 18 cases (40%), amphotericin B 7 cases (15.5%) and voriconazole 3 cases (6.6%). There were not significant differences between the two groups in relation to prescription of antifungal drugs.

Inadequate antifungal treatment was administered in 29 episodes occurring in elderly patients. In seven cases no treatment was prescribed at all (15%). Four patients with no suspicion of candidaemia died before the blood culture results were received. Adequate antifungal therapy was prescribed more frequently in younger patients but the rate of central venous catheter removal was similar in both groups (table 1). The mortality during the hospital admission (55.6%) was higher in elderly patients than in non-elderly patients (36.8%; $p=0.037$) (table 1).

DISCUSSION

A retrospective study of candidaemia in elderly patients is presented illustrating the high mortality of this condition. The most remarkable finding was that elderly patients were more likely to receive inadequate antifungal treatment or even no treatment. Therefore, strategies focused on improving diagnosis and appropriate management should be implemented to ameliorate this distressing situation.

As has been demonstrated in other studies, a high proportion of candidaemia episodes are detected in elderly patients (32.1% in our series)⁴. Therefore, it seems reasonable that efforts should be directed to better delineate their clinical presentation profile, which could enhance clinical suspicion in appropriate cases (table 1). On the other hand, the percentage of male gender among elderly patients with candidaemia may be explained by the shorter life expectancy among men¹⁴.

As could be expected, fewer patients with HIV infection, solid neoplasm and organ transplantation were detected among elderly patients^{5,7,12}. Therefore, searching for certain risk factors for candidaemia would be less rewarding than in younger patients. Other determinants, such as undergoing central line catheterization or parenteral nutrition, were more frequently detected in elderly patients in other series but not in our study^{5,7,12}. Finally, other risk factors, such as prior antibiotic treatment or prior abdominal surgery were not influenced

by age as described in other published studies^{7,12}. All these characteristics may increase the difficulty in suspecting candidaemia in these patients.

Issues that are still not resolved are the influence of advanced age on the proportion of *Candida* species and whether the empiric treatment should be different in elderly patients. In our series, there was a higher proportion of bloodstream infections due to *C. parapsilosis* among non-elderly patients. The greater use of central catheters and pretreatment with echinocandins could justify this finding^{15,16}. The difference in percentage of *C. glabrata* in elderly patients (19.6%) versus younger patients (11.3%) did not reach statistical significance. However, some authors have conclusively detected more cases due to *C. glabrata* in patients with advanced age, frequently associated with worse prognosis¹⁴. Other authors have found an increased incidence of candidaemia by *C. tropicalis*, which suggests a great variability of the predominant species causing candidaemia in the different studies⁵. Our results may encourage the use of fluconazole in elderly patients. Nevertheless, *C. parapsilosis* bloodstream infections treated with echinocandins did not present higher mortality than those treated with fluconazole in a previous study¹⁶.

Significant differences in the type of antifungal drugs used according to patient age were not observed. A previous study found more frequent use of azoles in elderly patients and of amphotericin B in children (related to frequent eye and central nervous system involvement in paediatric population)^{6,17}. In our series the administration of amphotericin B comparable in both groups, probably due to little concern about nephrotoxicity^{18,19}.

According to previous studies, elderly patients were more likely to receive inadequate antifungal treatment, or even no treatment at all^{6,7,13}. Improving this situation represents a clear objective for the future. A low expectation of presenting candidaemia may interfere with adequate patient management, as has previously been observed²⁰. In fact, "classic" risk factors, central venous catheters, parenteral nutrition or mechanical ventilation, were identified less commonly in elderly patients. Another element for the suboptimal management of candidaemia was the terminal state of some elderly patients, which gave rise to a limitation of the therapeutic effort⁷. It should be noted the reduced percentage of elderly patients with candidaemia who were submitted to fundoscopy. This issue in the management of patients with candidaemia should be improved given the high risk of developing chorioretinitis²¹.

Another finding of this study was the higher mortality observed in elderly patients, a poor outcome that has been observed in several previous studies^{6,7,22,23}. Greater patient fragility, immunosenescence or a high incidence of comorbidity, such diabetes or heart failure, may justify this result to a certain extent^{17,24-26}. The higher severity associated with advanced age, as observed in other studies, may be related to certain differences in the type of institution, the age required for a patient to be considered as elderly, or the underlying diseases^{5,13}.

Our study presents several limitations. The first is that

the age thresholds to be considered elderly in previous studies were not analogous to those determined here, which may reduce the validity of comparisons between different series. In fact, the clinical characteristics of patients in our series were quite different from those of previous studies. Another limitation was that attributable mortality was not analyzed. However, the differences in mortality between both groups were so pronounced that it clearly suggests a negative impact of advanced age and inadequate treatment in the prognosis of the episodes of candidaemia. Finally, the reduced number of patients and the retrospective nature of the study could have prevented from detecting more differences between the two groups of patients

CONFLICT OF INTEREST

None to declare

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