



ORIGINAL ARTICLE

Effect of the implementation of clinical guidelines on management of candidemia in elderly patients

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Abstract

Introduction: Mortality from candidemia is higher in elderly population than in younger patients, which may be related to suboptimal management. The aim of the present study is to evaluate adherence to the recommendations for the clinical management of candidemia in a population over 75 years before and after implementing specific training.

Patients and Methods: We recorded retrospectively data from candidemia episodes in elderly patients during two periods of time: 2010–2015 years (before training) and 2017–2022 years (after training), as well as adherence to the recommendations of the clinical practice guidelines, mortality and consultation to infectious disease specialists.

Results: Forty-five episodes of candidemia were recorded in the first period and 29 episodes in the second period. A better compliance to the recommendations of the clinical practice guidelines was observed in the second period: echocardiogram performance (75.9% vs. 48.9% $p = .021$), fundoscopy (65.5% vs. 44.4% $p = .076$), follow-up blood cultures (72.4% vs. 42.2% $p = .011$), removal of central venous catheter (80% vs. 52.9% $p = .080$) and adequate antifungal treatment (82.6% vs. 52.6% $p = .018$). A trend towards lower mortality was observed during the second period (27.6% vs. 44.4% $p = .144$).

Conclusion: The improvement of knowledge of clinical guidelines on candidemia and the participation of infectious disease specialists may increase the quality of care in elderly patients with candidemia. It would be necessary to enlarge the sample size to evaluate the real impact of this intervention on mortality.

KEYWORDS

Candida, candidaemia, candidemia

1 | INTRODUCTION

Candidemia is an invasive fungal infection relevant both for its frequency and mortality. *Candida* species are the sixth most commonly isolated microorganism in blood cultures.¹ Attributable mortality is between 30 and 60% according to different studies.² Adequate clinical management can significantly improve the prognosis of this infection.^{3,4}

It should be noted that in recent years there has been a notable demographic change in developed countries characterised by the progressive aging of the population. So much so, that it has been proposed to modify the age that defines this population, increasing the age limit from 65 to 75 years.⁵ It has been proven that candidemia in elderly patients presents a higher mortality than in younger patients,^{6,7} which has been related to a possible suboptimal clinical management.⁸ Fortunately, different clinical guidelines for the management of candidemia and various scales have been developed in recent years that make it possible to assess the degree of adherence to their recommendations. Notable among them are those developed by scientific societies such as ECMM (European Confederation of Medical Mycology) or GEMICOMED (Medical Mycology Study Group).^{9,10}

The aim of this study was to compare adherence to the recommendations on the clinical management of candidemia in the elderly and its prognosis before and after cross-sectional training on the content of the aforementioned guidelines. Likewise, it was intended to evaluate if the evaluation by an infectious disease consultant (IDC) supposes an additional positive factor in the adequate management of this infection.

2 | PATIENTS AND METHODS

We conducted a retrospective cohort study in a single tertiary centre in Madrid (Spain). All patients older than 75 years with positive blood cultures for *Candida* spp. during two different time periods were included: the first period was from January 2010 to September 2015; and the second was from January 2018 to December 2022. In cases in which the same patient had more than one episode of candidemia, only the first was considered.

The intervention consisted of implementing the diffusion of the measures recommended by GEMICOMED for candidemia⁹ by conducting clinical sessions in all clinical departments and clinical advice by infectious diseases expert in the event that it was requested by the responsible physician. The clinical sessions took place during the years 2016 and 2017 and were taught by three members of the infectious diseases' unit. In them, the recommendations for clinical management of these infections were reviewed and the way to contact the members of the aforementioned unit was provided.

Blood cultures were drawn following standard procedures and incubated on BACTEC 9240 and Bactec FX (Becton Dickinson™) automated systems. Definitive identification and antifungal susceptibility tests were confirmed using molecular biology techniques at

the reference microbiology centre (Carlos III Health Institute) during the first period, while in the second period identification was obtained through MALDI-TOF MS (Bruker Daltonics™). Antifungal susceptibility was determined by E-test between 2010 and 2011 and Sensititre Yeast One® (Thermo Scientific™) from 2011 onwards. The susceptibility criteria for all species were defined by the EUCAST guidelines in force in each period of the study. From 2020, these criteria were modified defining category 'I' as a susceptible species but with the administration of the antifungal treatment at high doses.¹¹

Data were collected from the centre's electronic record and included demographic data, comorbidities, microbiological and management data including fundus examination, echocardiogram, central venous catheter (CVC) removal, and dose and duration of antifungal treatment as well as evaluation by infectious diseases expert. Antifungal treatment was considered adequate if the *Candida* species was sensitive and if it was administered at the correct dose and within the first 48 h after obtaining positive blood cultures.

Quantitative variables were described as median and interquartile range, while categorical variables as percentages (%). Episodes of candidemia in patients aged 75 years or older were included. For the univariate analysis, the chi-square test (or the Fisher test when necessary) and Kruskal–Wallis were used for categorical and quantitative variables, respectively. The statistical significance value was established with a $p < .05$. All statistical analysis were done using Stata/BE software version 17.0 (STATA Corp.).

The study was approved by the local research ethics committee, which waived the need to obtain informed consent as it was a retrospective study.

3 | RESULTS

A total of 74 episodes of candidemia in the elderly were collected, 45 of them in the period 2010–2015 and 29 in the period 2017–2022. These episodes represented 32.1% of all candidemias during the first period and 27.4% during the second period ($p = .418$).

The mean age of the first period was significantly higher than the mean age of the second period [83.4 years, standard deviation (SD) 5.11 vs. 80.2 SD 4.50; $p = .007$], and the proportion of men significantly higher during the period 2017–2022 (82.7%) than during the period 2010–2015 (42.2%; $p = .007$). The Charlson comorbidity index (CCI) was lower in the second period compared to the first (5 points, interquartile range [IQR] 3–6 points vs. 6 points IQR 6–8; $p = .007$). The severity of the episodes, assessed using the PITT bacteremia score (PBS),¹² was similar in both periods (median 1 IQR point 0–3 points vs. median 1 IQR point 0–2 points; $p = .786$).

The most commonly identified *Candida* species during both periods was *C. albicans* (50% of the total isolates), followed by *C. glabrata* (21.6%) and *C. parapsilosis* (18.9%). During the second study period, there was a trend towards a greater number of episodes of candidemia due to *C. parapsilosis* compared to the first (27.6% vs. 13.3%; $p = .126$). Global susceptibility to fluconazole has remained stable over time, although the number of species with intermediate

susceptibility has increased (6.7% in the first versus 20.7% in the second period; $p=.072$). The number of species considered resistant has decreased in the second period compared to the first, not reaching statistical significance (13.3% in the first versus 6.9% in the second $p=.384$). The demographic and microbiological data of the patients studied are shown in Table 1.

Regarding the management of the episode, our study revealed greater adherence over time to the recommendations of the current clinical guidelines, with a higher percentage of patients implementing echocardiograms (75.9% vs. 48.9% $p=.021$), fundoscopy examination (65.5% vs. 44.4% $p=.076$), follow-up blood cultures (72.4% vs. 42.2% $p=.011$) and central venous catheter removal (80% vs. 52.9% $p=.08$), when the patient was a carrier of this device. Attending to the treatment, most of the patients received antifungal treatment (82.8% in the first period vs. 86.4% in the second period, $p=.674$), however only 52.6% of them were considered adequate during the period 2010–2015, compared to 82.6% from 2017 to 2022 ($p=.018$).

Overall mortality, mortality at 7 and at 30 days, was slightly lower in the second period compared to the first, without reaching statistical significance (48.9% vs. 37.9%; $p=.355$, 35.6% vs. 20.7%; $p=.172$, 44.4% vs. 27.6% $p=.144$, respectively). The data related to management, treatment, and mortality are included in Table 2.

We did not observe a relevant difference in the proportion of patients who were attended by an IDC in the most recent time period of time (37.9% vs. 26.7%; $p=.307$). During the first study period (2010–2015), patients followed by IDC had a better overall adherence to

the recommendations of the clinical guidelines. Compared to those who did not have such follow-up, a greater number of patients implementing echocardiograms (83.3% vs. 36.4%; $p=0.005$), fundoscopy examination (75% vs. 33.3%; $p=.013$); follow-up blood cultures (66.7% vs. 33.3%; $p=.045$), CVC removal (75% vs. 21.4%; $p=.014$) and appropriate treatments (91.7% vs. 27.3%; $p<.001$) were identified in this group. In the second period between 2017 and 2022, greater adherence to the recommendations was also found among patients followed up by IDC, although the differences with those who did not have such follow-up were not statistically significant (Table 3).

4 | DISCUSSION

The present study demonstrates that the diffusion of recommendations on the proper management of candidemia in elderly patients improves the quality of care received by these patients.

We have followed the European Confederation of Medical Mycology (ECMM) Quality (EQUAL) Standard that was developed as a score that quantifies the degree of adherence to the recommendations of the clinical guidelines for the management of candidemia. The variables included in the score are ophthalmological examination, echocardiogram, central venous catheter removal when present, empiric treatment with echinocandins, and follow-up blood cultures.⁹

Some previous studies have shown lower scores on this scale in patients older than 75 years compared to younger patients,¹⁴ which in turn has been associated with an increase in mortality.¹⁵ In our patients, we observed better compliance with clinical management recommendations as a result of the communication of information about this condition throughout the hospital.

In our series, the percentage of patients with CVCs was higher in the period 2017–2022 compared to 2010–2015 (69% vs. 37.8% $p=.009$), like that described in previous works.¹⁶ In addition, the degree of comorbidity (quantified through the CCI) was lower in the second follow-up period. The possible lower number of patients in a more advanced stage of their underlying disease in whom the therapeutic effort could have been limited may have influenced better compliance with the recommendations for this infection.

Previous studies have shown that follow-up of candidemia by an IDC improves compliance with the recommendations of clinical guidelines, and even its prognosis.^{17,18} In other infectious pathologies, such as endocarditis (in which candidemia may be involved), experts and consensus documents agree on the need for support and follow-up through IDC.¹⁹ In the present study, it was observed that in both periods the patients with IDE follow-up had better management than those in whom there was no follow-up, although this did not significantly impact mortality. This is an expected result since IDEs treat more cases of this pathology and accumulate greater knowledge and experience in its management.^{20,21}

TABLE 1 Demographic, clinical and microbiological data of candidemia episodes in the elderly between 2010–2015 and 2017–2022.

	2010–2015 period N=45	2017–2022 period N=29	p-Value
Male	19 (42.2%)	24 (82.7%)	.001
Mean age	83.4 (SD 5.11)	80.2 (SD 4.5)	.007
CCI (median–IQR) ¹³	6 (6–8)	5 (3–6)	.007
PBS (median–IQR)	1 (0–3)	1 (0–2)	.786
Isolated species			
<i>C. albicans</i>	24 (53.3%)	13 (44.8%)	.475
<i>C. parapsilosis</i>	6 (13.3%)	8 (27.6%)	.126
<i>C. glabrata</i>	10 (22.2%)	6 (20.7%)	.876
<i>C. tropicalis</i>	2 (4.4%)	0	.250
<i>C. guilliermondii</i>	2 (4.4%)	0	.250
<i>C. dublinensis</i>	1 (2.2%)	0	.419
<i>C. lusitaniae</i>	0	1 (3.5%)	.210
<i>C. ortopsilosis</i>	0	1 (3.5%)	.210
Azole susceptible	36 (80%)	21 (72.4%)	.449
Azole intermediate	3 (6.7%)	6 (20.7%)	.072
Azole resistant	6 (13.3%)	2 (6.9%)	.384

Abbreviations: CCI, Charlson Comorbidity Index; IQR, Interquartile Range; PBS, Pitt Bacteremia Score; SD, Standard deviation.

	2010–2015 period N = 45	2017–2022 period N = 29	p-Value
Echocardiogram	22 (48.9%)	22 (75.9%)	.021
Funduscopy	20 (44.4%)	19 (65.5%)	.076
Follow-up blood culture	19 (42.2%)	21 (72.4%)	.011
CVC	17 (37.8%)	20 (69%)	.009
CVC removal	9/17 (52.9%)	16/20 (80%)	.080
IDC	12 (26.7%)	11 (37.9%)	.307
Antifungal treatment	38 (86.4%)	24 (82.8%)	.674
Adequate treatment	20/38 (52.6%)	19 / 24 (82.6%)	.018
Overall mortality	22 (48.9%)	11 (37.9%)	.355
48 h mortality	5 (11.1%)	1 (3.5%)	
7-days mortality	16/45 (35.6%)	6/29 (20.7%)	.172
30-days mortality	20/45 (44.4%)	8/29 (27.6%)	.144

TABLE 2 Univariate comparison of the management, treatment and mortality of elderly patients with candidemia between 2010–2015 and 2017–2022.

Abbreviations: CVC, central venous catheter; IDC, infectious diseases consultation.

TABLE 3 Comparison of adherence to recommendations in patients with IDC during 2010–2015 and 2017–2022.

	2010–2015 period N = 45			2017–2022 period n = 29		
	Cases without IDC N = 33	Cases with IDC N = 12	p-value	Cases without IDC N = 18	Cases with IDC N = 11	p-Value
Echocardiogram	12 (36.4%)	10 (83.3%)	0.005	12 (66.7%)	10 (90.9%)	.139
Funduscopy	11 (33.3%)	9 (75%)	0.013	10 (55.6%)	9 (81.8%)	.149
Follow-up blood cultures	11 (33.3%)	8 (66.7%)	0.045	12 (66.7%)	9 (81.2%)	.376
CVC removal	3/22 (21.4%)	6/22 (75%)	0.014	10 (66.7%)	7 (63.4%)	.873
Adequate treatment	9 (27.3%)	11 (91.7%)	0.000	11 (64.7%)	10 (90.9%)	.118

Abbreviations: CVC, central venous cathete; IDC, infectious diseases consultation.

During the second period, the degree of adherence to the measures increased both in patients followed by IDC and in those without such follow up, possibly reflecting the positive impact of diffusion measures for proper candidemia management carried out in the hospital since 2017.

The overall mortality of elderly patients with candidemia is high and higher than that of young patients.^{7,22} Previous studies estimate the mortality of candidemia in the elderly between 30% and 50%, which coincides with the data collected in our series.^{6,7,14,23} Unfortunately, our work has not been able to demonstrate that the improvement in the management of candidemia has a direct impact on the mortality of elderly patients. Although statistical significance has not been reached, a trend towards lower early and late mortality is observed in the second follow-up period, which is consistent with data previously published in other series, in which bundles of care for the management of candidemia has been shown to improve the prognosis of patients.^{24–26} The lack of statistical significance can probably be explained by the small sample size of the second period. It must also be clarified that we have not found the reason that justifies younger age and less comorbidity during the second period. It is possible that the COVID-19 pandemic has influenced this fact.^{13,27} Likewise, it should be noted that the death can also be related to advanced age, exacerbations of the underlying pathology or

other complications that reduce the effect of antifungal treatment on mortality.

Our study has several limitations. Firstly, it is a retrospective study with the interpretation biases that this entails. Second, we have reported candidemia episodes from only one centre, so external validation of the results may be questionable. Finally, it is common for the management of elderly patients to establish therapeutic restrictions or abstentions and palliative management in the context of end-of-life situations, which can act as a confounding factor when interpreting the results.

In conclusion, in our area, the degree of adherence to the recommendations of the clinical guidelines in the management of candidemia in the elderly has improved substantially after the implementation of educational activities, as has the surveillance and follow-up by IDC. It would be advisable implementing a study with a larger sample size to demonstrate that adherence improves the prognosis of elderly patients with candidemia. In any case, it is encouraging that there has been a substantial improvement in the management of candidemia in elderly patients over time.

AUTHOR CONTRIBUTIONS

Natalia Vicente Lopez: Conceptualization; writing – original draft; formal analysis; investigation. **Jorge Calderon Parra:** Data

curation; software; project administration. **Alejandro Muñoz Serrano:** Investigation. **Andrea Gutiérrez Villanueva:** Investigation. **Sara de la Fuente Moral:** Visualization. **Victor Moreno-Torres:** Methodology; supervision. **Elena Muñoz Rubio:** Writing – review and editing; validation. **Antonio Ramos Martínez:** Writing – review and editing; funding acquisition; resources.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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