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Note

Isolation of *Candida auris* in large hospitals in the Autonomous Community of Valencia; population-based study (2013–2017)

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ABSTRACT

Background: *Candida auris* is an emerging multidrug-resistant and highly virulent yeast that spreads easily among patients.
Aims: To describe the characteristics of candidemia caused by *C. auris* in the southeast of Spain (Autonomous Community of Valencia – ACV) through a 5-year population-based study.
Methods: An analysis of all the episodes of candidemia diagnosed in the ACV, with approximately 4,500,000 inhabitants, during 2013–2017, was done. Data were obtained from the Epidemiological Surveillance Valencian Network, a network that collects all the microbiological data from the hospitals in the study region.
Results: Based on the records, 1.9% of the isolates recovered from the positive blood cultures (corresponding to 1789 patients) were yeasts. This implies an annual rate of 7.09 cases/100,000 inhabitants. Of the 23 yeast species isolated, *Candida albicans* was the most frequent (37.3%), showing a higher frequency than *Candida parapsilosis* (28.4%) and *Candida glabrata* (15.6%) ($p < 0.0001$). It is remarkable the emergence of *C. auris* during 2016 and 2017, as this species became the fourth more prevalent in 2016 (9.2%), and the third in 2017 (15.7%). Fungemia was more common in hospitals with >500 beds (63.3% versus 36.7% in small hospitals) ($p < 0.0001$), and *C. auris* was mostly isolated in large hospitals (8.5% versus 0.3%); its incidence was higher in autumn and among the age group of 65–84 years.
Conclusions: The information about the local epidemiology of candidemia is essential in order to decide the best empirical treatment approach. This study reports the novel presence of *C. auris* in large hospitals. This pathogen has usually resistance to several antifungals and causes severe fungemia, so the results of this work reveal the need to monitor the presence of this species systematically.

Aislamiento de *Candida auris* en grandes hospitales en la Comunidad Valenciana; estudio poblacional (2013-2017)

Palabras clave:
Fungemia
Candida auris
Candidemia

RESUMEN

Antecedentes: *Candida auris* es una levadura multirresistente y virulenta que puede propagarse fácilmente entre los pacientes.
Objetivos: Describir las características de las candidemias causadas por *C. auris* en el sureste de España (Comunidad Valenciana) a través de un estudio poblacional de 5 años.

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Métodos: Se realizó el análisis de todos los episodios de candidemia diagnosticados en la Comunidad Valenciana, con aproximadamente 4.500.000 de habitantes, durante los años 2013-2017. Los datos se obtuvieron de la Red de Vigilancia Microbiológica de la Comunidad Valenciana, que recoge los datos de todos los hospitales de la región.
Resultados: Según los datos estudiados, un 1,9% de los aislamientos recuperados en hemocultivos (correspondientes a 1.789 pacientes) eran levaduras. Esto supone una tasa anual de 7,09 casos/100.000 habitantes. Se aislaron 23 especies de levaduras, *Candida albicans* fue la más frecuente (37,3%), con una frecuencia significativamente mayor que *Candida parapsilosis* (28,4%) y *Candida glabrata* (15,6%) (p < 0,0001). Es importante remarcar la aparición de *C. auris*, que se convirtió en la cuarta más prevalente en 2016 (9,2%), y la tercera en 2017 (15,7%). Las fungemias fueron más comunes en los hospitales grandes (63,3% > 500 camas versus 36,7% < 500 camas) (p < 0,0001). *C. auris* fue aislada en hospitales grandes (8,5 versus 0,3%), y su incidencia fue más alta en otoño y en el grupo de edad de 65-84 años.
Conclusiones: Disponer de información sobre la epidemiología de las candidemias es esencial para establecer el mejor tratamiento de forma empírica. Este estudio pone de manifiesto la presencia de *C. auris* en grandes hospitales. Este patógeno causa fungemias graves y suele presentar multirresistencia a los antifúngicos. Los resultados de este trabajo revelan la necesidad de evaluar su presencia en otras comunidades.

Invasive fungal infection is a serious illness that continues to change over time, and the emergence of *Candida auris* aggravates this health problem. Fungemia carries a high mortality rate, especially among vulnerable patients admitted to the intensive care units, but also among those using prostheses, catheters or other intravascular devices, and even those receiving immunosuppressant treatments, chemotherapy or transplant recipients.[14] Candidemia represents a threat to public health systems considering the large numbers of cases and the enormous expenditure. It has been estimated that, in the USA, hospitalizations due to *Candida* infections cost $1.4 billion.[1]

In this study, we describe the epidemiology of candidemia in the southeast of Spain, by the Mediterranean coast, through a 5-year population-based study. Besides, this work analyses the impact of the emergence of *C. auris* in several hospitals in the study region.

Patients and methods

Design

The work is a cross-sectional study to estimate the prevalence of candidemia. The results of the positive blood cultures reported from all public hospitals in the Autonomous Community of Valencia (ACV) (population: 4,397,476) between January 2013 and December 2017 were analysed.

Source of information

The data were obtained from "RedMIVA", a network connecting information from the microbiology laboratories of public hospitals in the ACV. One isolate per patient was studied. To estimate the annual incidence rate per 100,000 inhabitants, the information about the overall population was obtained from the official statistic census published by Valencian Autonomous Community Government (*Generalitat valenciana* – www.gva.es)

Statistical analyses

The categorical variables were expressed as counts (percentage) together with 95% confidence intervals (95% CI), and continuous variables as the mean and standard deviation (SD) or median and InterQuartile Range (IQR), as appropriate. The statistical differences among the groups were assessed using Chi-square or Fisher's exact test for categorical variables. For the continuous variables, the *t*-Student's test was applied. The alpha error was set at 0.05, and *p* values were two-tailed. All statistical analyses were conducted using the SPSS Statistics (IBM, version 22.0).

Results

During 2013–2017, yeasts were isolated from 1789 patients, accounting for 1.9% (95% CI 1.85–2.0) of the total positive blood cultures in the ACV. Twenty-three different species were identified; the five species more frequently isolated were *Candida albicans* (37.3%; 95% CI 35.1–39.6), *Candida parapsilosis* (28.4%; 95% CI 26.3–30.5), *Candida glabrata* (15.6%; 95% CI 13.9–17.3), *Candida tropicalis* (5.7%; 95% CI 4.6–6.8) and *C. auris* (5.5%; 95% CI 4.4–6.6) ($p < 0.0001$). (Table 1). *C. auris* was the fifth species more frequently isolated, although it was found only in the last two years. In 2016 its incidence was 9.2% (95% CI 6.3–12.1), and in 2017 it raised to 15.7% (95% CI 11.9–19.5).

The percentage of *C. albicans* gradually decreased along the years: 42.1% of the total yeast isolates in 2013 (95% CI 36.6–47.6), 43% in 2014 (95% CI 37.4–48.7), 37.8% in 2015 (95% CI 32.6–43.1), 33.3% in 2016 (95% CI 28.7–38.) and 32.5% in 2017 (95% CI 27.6–37.3). The 63.1% ($n = 1126$) (95% CI 60.9–65.4) of the total yeast isolates were recovered from men and 36.9% ($n = 658$) (95% CI 34.6–39.2) from women ($p < 0.0001$). The differences in the prevalence of the yeast species according to gender were minimal and not statistically significant (Fig. 1A).

Considering the age, the analysis revealed that many cases of candidemia occurred in patients aged 65–84 years (50.1% of the total yeast isolates; 95% CI 47.8–52.5), followed by those aged 45–64 years (29.1%; 95% CI 26.9–31.2), 18–44 years (9.9%; 95% CI 8.5–11.3), >85 years (5.6%; 95% CI 4.5–6.7), and <18 years (5.3%; 95% CI 4.2–6.3) ($p < 0.0001$). *C. parapsilosis* predominated in patients with less than 18 years (55.3%; 95% CI 44.7–65.9), while *C. albicans* did so in elderly patients (40.6%; 95% CI 30.5–50.7). *C. auris* was most frequent in patients of 18–44 years (15.3%; 95% CI 9.7–20.8) (Fig. 1B).

When considering the hospital size, the results revealed that 63.3% (95% CI 61.1–65.6) of the fungal species were isolated from hospitals with at least 500 beds, while 36.7% (95% CI 34.4–38.9) were isolated from smaller hospitals ($p < 0.0001$). In large hospitals, the prevalence of *C. albicans* and *C. parapsilosis* was similar (32.9% [95% CI 30.1–35.7] versus 32.4% [95% CI 29.6–35.2], respectively),

Table 1
Yeast species per year (the most isolated are in bold type).

	Year					Total
	2013	2014	2015	2016	2017	
Yeast isolates	328	316	349	414	382	1789
ACV population	5,117,190	5,129,266	5,011,797	5,004,171	4,974,769	5,047,439
Yeast rate per 100,000 inhabitants	6.4	6.16	6.96	8.27	7.67	7.09
Yeasts (%)						
Candida albicans	**42.1**	**43**	**37.8**	**33.3**	**32.5**	**37.3**
Candida auris	**0**	**0**	**0**	**9.2**	**15.7**	**5.5**
Candida dubliniensis	0	0	0	0.2	0	0.1
Candida famata	1.8	1.3	0.3	0.5	0.5	0.8
Candida glabrata	**14.3**	**15.5**	**17.5**	**17.1**	**13.4**	**15.6**
Candida guilliermondii	0	0	0.9	0.5	0.3	0.3
Candida haemulonii	0.3	0	0	0.7	0.3	0.3
Candida krusei	0.9	1.9	3.2	1.7	3.1	2.2
Candida lusitaniae	0.3	0.3	0.6	0.2	1	0.5
Candida magnoliae	0	0.3	0	0	0.3	0.1
Candida norvegensis	0.3	0	0	0	0.0	0.1
Candida orthopsilosis	0	0	0	0.5	1.8	0.5
Candida parapsilosis	**33.2**	**29.4**	**31.2**	**27.1**	**22.3**	**28.4**
Candida sake	0	0	0	0.2	0	0.1
Candida sphaerica	0	0	0	0	0.3	0.1
Candida spp.	1.5	2.8	1.7	1.4	2.6	2
Candida tropicalis	**4.6**	**5.1**	**6.6**	**6.8**	**5.2**	**5.7**
Geotrichum capitatum	0.3	0	0.3	0	0.3	0.2
Hanseniaspora opuntiae	0	0	0	0.2	0	0.1
Non identified yeasts	0	0	0	0	0.5	0.1
Rhodotorula mucilaginosa	0.3	0	0	0	0	0.1
Rhodotorula rubra	0	0.3	0	0	0	0.1
Saccharomyces cerevisiae	0	0	0	0.2	0	0.1

Bold values indicate the five species more frecuently isolated, including *C. auris* in the last years.

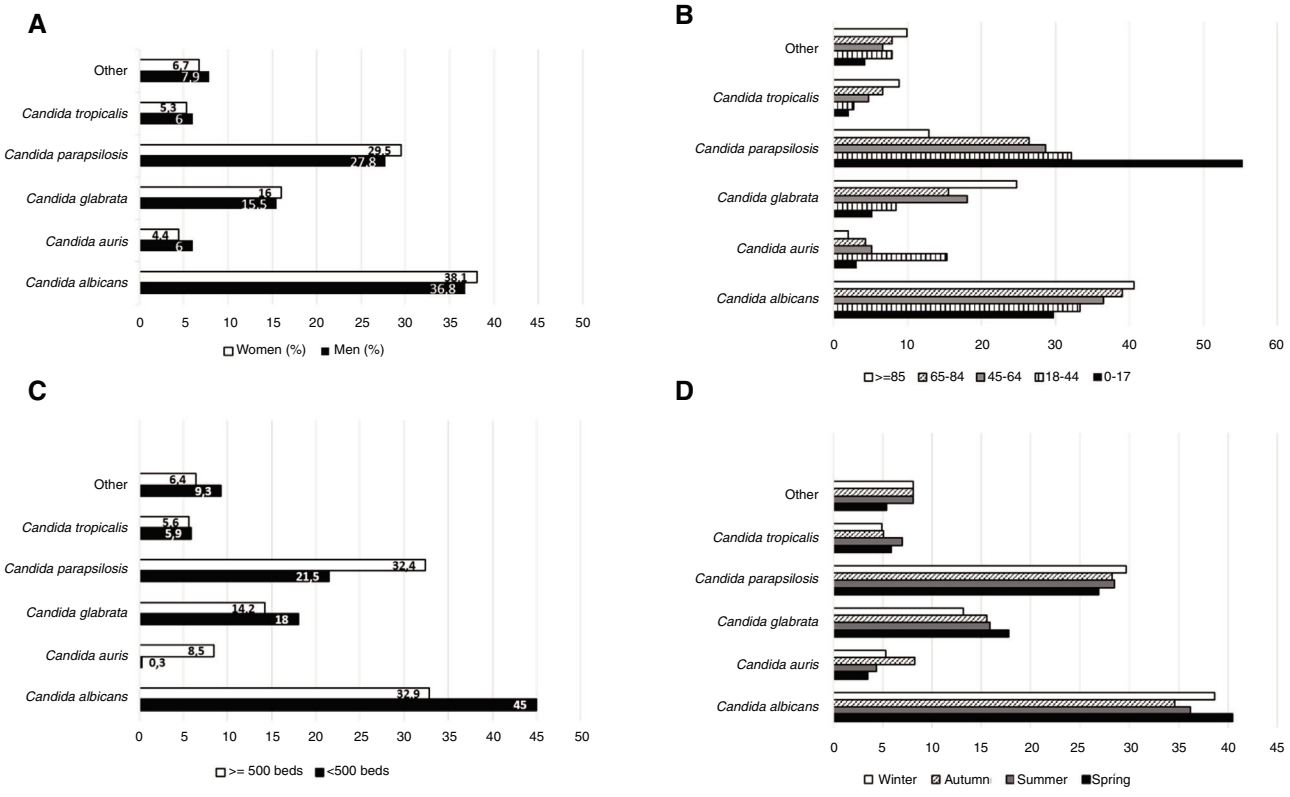

Fig. 1. Distribution (%) of yeast isolates according to sex (A), age (B), hospital size (C), and season (D).

while in small hospitals the frequency of *C. albicans* was twice that of *C. parapsilosis* (45%; 95% CI 41.1–48.9 versus 21.5%; 95% CI 18.3–24.7, respectively). Additionally, *C. auris* was primarily isolated in large hospitals, being the fourth-most prevalent species (8.5% of all; 95% CI 6.8–10.1), while it was scarcely found in small hospitals (0.3%; 95% CI 0.0–1.1) (Fig. 1C). At the end, the study showed that the prevalence of fungemia was not related to the season (Fig. 1D).

Discussion

A European study reported a candidemia incidence of approximately 79 cases/day; it was estimated that 29 patients had fatal outcomes on day 30.[7] In our study area, the annual prevalence of fungemia was 7.09 cases/100,000 inhabitants, which is higher than the European average (3.88 cases/100,000). These values highlight the importance of a better knowledge of this pathology in order to improve the empirical treatment.

C. albicans is the yeast most frequently isolated in candidemia,[6] and there are discrepancies in the prevalence of the other species. Some studies find that *C. glabrata is* the most common non-*C. albicans Candida* species among the high-risk units and across all geographic regions, except Latin America, where *C. parapsilosis* and *C. tropicalis* are more common.[13,16] Other studies reveal that after *C. albicans*, *C. parapsilosis* and *C. glabrata* are the species most frequently isolated, which agrees with our data.[2,4,17]

A decrease in the incidence of *C. albicans* but the increase of other yeast species incidence has been reported from other geographical areas, a fact probably due to a major use of azole drugs and a trend towards an increased antifungal resistance. Finally, the emergence of multi-resistant species, such as *C. auris* or *C. glabrata*, is a big threat that needs global surveillance of candidemia cases.[9,15] Yeast species other than *C. albicans* cause a long term candidemia (median 3 days vs. 1 day) after an effective antifungal regime, bringing to light a slower response to the antifungal treatment and a higher treatment failure rate than that for *C. albicans* candidemia.[10]

C. parapsilosis is the most prevalent species (55.3%) found among children, whereas *C. albicans* is the most frequent isolated in other patients. Moreover, the prevalence of *C. glabrata* among the elderly (age > 85 years) is high, although that of *C. albicans* is the highest (40.6%). The difference in the prevalence based on the age-group has also been reported for other geographical areas.[17] Our data differ from those of other geographical areas in which *C. albicans* was the most common pathogen causing invasive candidiasis among neonates and children (47.8% vs. 44.1% cases).[5]

C. auris has been reported as the fourth-most prevalent species in large hospitals of the study region, and its presence is associated with hospitals with more than 500 beds. This data radically modified the approach of this pathology as the pathogen is resistant to several antifungal agents, is highly virulent and spreads easily among patients.[18] A similar phenomenon has been reported for the rest of Europe during 2013–2017, with 620 cases of *C. auris* reported in the European Union/European Economic Area (110 cases of bloodstream infections), which is generally associated with large outbreaks.[3,8]

The severity of this pathology, its heterogeneity and the appearance of new species of yeasts is often associated with resistance to multiple antifungal agents, which makes a fast identification of the microorganism involved in each process critical. Therefore, the development of a mixed expert panel comprising specialists in clinical microbiology and infectious diseases is mandatory for the appropriate management of such serious pathology, based on the information sourced about the local epidemiology of these pathogens.[11,12]

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Conflict of interests

Authors declare no conflict of interest.

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