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Artículos originales

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Epidemiología de los casos de candidemia en un hospital universitario en Colombia, 2008-2014

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Abstract: **Introduction:** Candida species are commensal yeasts of the human microbiota. However, due to several host's conditions, bloodstream infections may arise causing high morbimortality. **Methods:** Retrospective cross-sectional analytical study of positive blood cultures for *Candida* spp. between 2008-2014 at a university hospital in Bogota, Colombia. We evaluated clinical and microbiological characteristics prior to the first positive blood sample was obtained and determined associations with non-*C. albicans* (NCA) species infections. **Results:** We included 123 candidemia cases. *C. albicans* was the most frequently isolated species (42%). However, NCA species as a group were observed more often. Over 70% of cases were managed at the ICU, with a median stay of 14 days. Several medical factors were frequently observed, however none appeared to be associated with NCA species candidemia. Resistance to at least one antifungal agent was observed in 29% of cases, although a reduced sample of susceptibility tests was available. **Conclusions:** Our results support a worldwide shift towards NCA candidemia. However, clinical features were not associated with NCA infections. The identification of risk factors and the improvement of prediction scores must be prioritized, in order to identify patients at high risk who may benefit of pre-emptive therapy.

Keywords: candida, candidemia, fungal drug resistance, epidemiology, risk factors.

Resumen: **Introducción:** *Candida* spp. es una levadura comensal de la microbiota humana. Por características del hospedero, las infecciones del torrente sanguíneo pueden aparecer y causar una gran morbimortalidad. **Métodos:** Estudio restrospectivo transversal analítico de los cultivos positivos para *Candida* spp. entre 2008 y 2014 en un hospital universitario en Bogotá, Colombia. Se evaluaron las características clínicas

y microbiológicas presentes previo a la toma de la primera muestra de sangre positiva y se determinaron asociaciones con infecciones por especies no *C. albicans* (NCA). **Resultados:** Se incluyeron 123 casos de candidemia. *C. albicans* fue la especie más aislada (42 %). Sin embargo, las especies NCA como grupo fueron observadas más frecuentemente. Más del 70 % de los casos presentaron manejo en la unidad de cuidado intensivo, con una mediana de estancia de 14 días previo a la primera muestra de sangre positiva. Se detectaron numerosas características médicas; sin embargo, ninguna estuvo asociada con candidemia por especies NCA. Se observó resistencia a por lo menos un antifúngico en el 29 % de los casos, aunque en una muestra reducida de pruebas de sensibilidad. **Conclusiones:** Nuestros resultados sustentan el viraje mundial hacia la candidemia por especies NCA; pero no encontramos asociaciones clínicas en este grupo. Debe dársele prioridad a la identificación de factores de riesgo y a la optimización de los puntajes de predicción, que permitan identificar pacientes en riesgo que se beneficien de terapia preventiva.

Palabras clave: Candida, candidemia, farmacorresistencia fúngica, epidemiología, factores de riesgo.

Introduction

Candida spp. constitute the most common fungal agents causative of invasive disease in hospitalized patients (1). Candidemia is defined as the presence of the yeast in the bloodstream (2). It is considered the 4th cause of septicemia in hospitalized patients in the USA (3) with a mortality rate of up to 60%, thus surpassing mortality due to bacteremia (4,5,6). It is associated with a longer hospital stay and a high economic burden to healthcare systems, which may sum up to USD 40.000 per patient (4,7). Blood cultures are the mainstay diagnostic gold standard (2), however their performance appears to be low, with a false negative rate close to 50% (7). Candidemia incidence is rising worldwide, probably due to immunosuppressive therapies, organ transplantation, surgical interventions, and an aging population with multiple comorbidities (7,8,9). Its main etiological agent is *C. albicans*, although a shift towards non-*C. albicans* (NCA) species with a reduced antifungal susceptibility is increasingly observed (3,4,7), which makes candidemia a major public health issue. More than 90% of candidemia cases present one of these species: *C. albicans, C. glabrata, C. tropicalis, C. parapsilosis* or *C. krusei* (10).

Incidence has been steady in high-income countries. Nevertheless, it has been rising in middle and low-income regions, such as Latin America (7). Several factors have been associated to candidemia, such as malignancies, diabetes, kidney disease, neutropenia, pancreatitis, Human Immunodeficiency Virus (HIV) infection, major surgery, mechanical ventilation, parenteral nutrition, chemotherapy, corticosteroids, and immunosuppression (11). A number of predictive rules and scores are available, which may identify high risk patients that may benefit of pre-emptive therapy (11,12,13,14,15). Since the 90s (7), a worrisome shift towards NCA candidemia is increasingly observed worldwide. Thus, we aimed to describe the epidemiologic profile of candidemia cases at our institution and to assess clinical associations with the development of NCA species candidemia.

Methods

Patient enrollment and data collection

We conducted a retrospective cross-sectional analytical study using the registry of positive blood cultures between January 2008 and January 2014 at a University Hospital in Bogota, Colombia. Candidemia cases managed at our university hospital and confirmed by a positive blood culture were included. Candidemia cases without microbiologic confirmation were excluded. When susceptibility tests were available, antifungal resistance profile was assessed.

Study variables

Based on previously reported risk factors (16), clinical and microbiologic characteristics were included: *Candida* species, susceptibility profile, patient's age, gender, and clinical characteristics present prior to obtaining the first positive sample. The clinical characteristics included were diabetes, hematologic or solid malignancies, chemotherapy, kidney disease (acute or chronic), HIV, corticosteroids, biologic therapy, neutropenia, days of stay at the Intensive Care Unit (ICU), parenteral nutrition, mechanical ventilation, surgical intervention, pancreatitis and prior use of broad spectrum antibiotic or antifungal therapy.

Statistical analysis

Categorical variables were expressed as absolute and relative frequencies, whereas continuous variables were expressed as medians and interquartile ranges. Due to the study design, to establish associations and to measure their magnitude, contingency tables were determined and indirect relative risks with their confidence intervals were determined. To perform analysis, Stata (v.14) for Windows was used. The study was approved by our institution's Ethics and Research Committee.

Results

One-hundred twenty-three candidemia cases were obtained, out of which 53.7% were present in women. Table 1 presents the sample's demographic and clinical characteristics. A median age of 55 years (IQR 34-70 years) was observed for the general sample. Most of the cases were present in patients between 15 and 60 years (57%), whereas less than 5% were detected in patients younger than 1 year.

Table 1
Demographic and clinical characteristics by isolated species

Variable	Total % (n) n= 123	*C. albicans* % (n) n=52	NCA % (n) n= 71	Indirect Relative Risk
Median age (years) [IQR]	55 [34-70]	53.5 [38,2-70]	55 [29-70]	-
Age subgroups				NA
0-14 years ≤ 1 years	9 (11) 4 (5)	18 (2) 0 (0)	82 (9) 7 (5)	- -
15-60 years	57 (70)	44 (31)	56 (39)	-
> 60 years	34 (42)	45 (19)	55 (23)	-
Male patients	46 (57)	52 (27)	42 (30)	1.45 (0.67-3.23)
HIV	6 (8)	4 (2)	8 (6)	0.43 (0.04-2.57)
Corticosteroids	36 (44)	35 (18)	37 (26)	0.92 (0.4-2.06)
Biologic therapy	4 (5)	10 (5)	0 (0)	NA
Hematologic malignancy	21 (26)	19 (10)	22 (16)	0.82 (0.29-2.15)
Solid malignancy	20 (25)	25 (13)	17 (12)	1.64 (0.61-4.37)
Chemotherapy	24 (29)	19 (10)	27 (19)	0.65 (0.24-1.67)
Diabetes	18 (22)	17 (9)	18 (13)	0.93 (0.32-2.61)
Kidney failure	43 (53)	40 (21)	45 (32)	0.83 (0.37-1.81)
Neutropenia	24 (29)	17 (9)	28 (20)	0.53 (0.19-1.38)
ICU stay Median stay (days) [IQR]	71(88) 14 [6-21]	71 (37) 14 [4-20.5]	72 (51) 14 [6-21]	0.97 (0.41-2.32) -
Broad spectrum antibiotics	99 (122)	100 (52)	99 (70)	NA
Parenteral nutrition	41 (51)	38 (20)	44 (31)	0.81 (0.36-1.78)
Mechanical ventilation	64 (79)	56 (29)	70 (50)	0.53 (0.23-1.19)
Surgical intervention	80 (99)	77 (40)	83 (59)	0.68 (0.25-1.84)
Antifungal therapy	21 (26)	15 (8)	25 (18)	0.53 (0.18-1.45)
Pancreatitis	4 (5)	4 (2)	4 (3)	0.91 (0.07-8.23)
Total	100 (123)	42.3 (52)	57.7 (71)	

IQR: Inter-quartile range; NCA: Non-Candida albicans species; HIV: Human Immunodeficiency Virus; ICU: Intensive Care Unit; NA: Not applicable due to statistical approach.

Regarding clinical characteristics prior to obtaining the first positive blood sample, most patients received broad spectrum antibiotic therapy (99%). Further, previous surgical intervention and mechanical ventilation were rather common, being present in 80% and 64% of cases, respectively. Over 70% of patients were managed at the ICU, with a median of 14 days prior to obtaining a positive blood sample. Over a third of cases presented kidney disease, received parenteral nutrition or corticosteroids. Interestingly, up to one quarter of patients received antifungal therapy, chemotherapy, presented neutropenia, or had diabetes. Less than 10% of patients were HIV positive or presented pancreatitis. Up to 40% of patients presented a medical history of either hematologic or solid malignancy. No differences were observed between C. albicans and NCA species cases.

As shown in Table 2, in patients with malignancies, NCA species were more frequently isolated (55%). *C. tropicalis* (20%), *C. parapsilosis* (12%) and *C. krusei* (8%) were the most often observed species.

Table 2
Distribution (%) of Candida species by malignancy type

Species	Total	Head and Neck	GI	Lung	GU	Hematologic	Other
C. albicans	23 (45)	3	5	1	2	10	2
NCA	28 (55)						
C. tropicalis	10 (19.7)	1	1	-	1	7	-
C. parapsilosis	6 (11.8)	1	1	-	1	2	1
C. krusei	4 (7.8)	-	1	-	-	3	-
C. glabrata	2 (3.9)	2	-	-	-	-	-
C. guillermondi	3 (5.9)	-	1	-	-	2	-
C. inconspicua	2 (3.9)	1	-	-	-	1	-
C. lusitaniae	1 (2)	-	-	-	-	1	-
Total	51 (100)	8 (31)	9 (18)	1 (2)	4 (8)	26 (51)	3 (6)

GI: Gastrointestinal; GU: Genitourinary.

The most frequent species was C. albicans (42%). As a group, NCA species were more often observed (58% vs 42%). Susceptibility profiles were available for 21 cases (17%) and up to 29% of cases were resistant to at least one antifungal agent (Table 3).

Table 3
Susceptibility profile (%)

	Total	Multi-sensible	Fluconazole*	Itraconazole	Voriconazole*
C. albicans	13 (62)	10	3	-	2
NAC	8 (38)	-	-	-	-
C. glabrata	1 (5)	1	-	-	-
C. tropicalis	3 (14)	2	-	-	1
C. parapsilosis	3 (14)	2	-	1	-
C. krusei	1 (5)	-	1	-	-
Total	21 (100)	15 (71)	3 (14)	1 (5)	2 (10)

* Two C. albicans isolates were resistant to both fluconazole and voriconazole.

Discussion

Although the most frequently isolated species was *C. albicans*, a shift towards NCA species was detected when species were analyzed as a group. Several medical factors were frequently observed in candidemia cases, however none of them appeared to be associated with NCA species candidemia. The median stay in the ICU prior to a positive blood sample was 14 days.

Candida species isolation may be analyzed from two viewpoints. On the one hand, when single species isolations are analyzed, *C. albicans* is the most frequently isolated species (17,18,19,20,21,22,23,24,25). On the other hand, when *C. albicans* and NCA species are compared, the latter reveals a clear dominance worldwide (17,18,26,27,28,29,30). However, since the 90s, a shift towards NCA candidemia is increasingly observed (7). Previous epidemiological data in our country (6,9,27,31,32) reported a high frequency of C. parapsilosis and *C. tropicalis*.

Several risk factors for candidemia have been reported and were included in our study (16). Previous descriptions showed a higher frequency of candidemia in extreme of ages (i.e., younger than one year or older than 65 years) (7,24), whereas our data present a higher frequency between 15- and 60-year-old patients. Regarding ICU stay, a previous Colombian study in non-neutropenic patients reported clinical risk factors associated with candidemia, namely a hospital stay over 25 days, previous use of meropenem, abdominal surgery and hemodialysis (33). No differences in mortality rates were observed when compared to controls. In addition, Cortés et al. (6) reported that most patients presented a prolonged ICU stay with a mean of 29 days. However, we must point out that the applied methodology differs from ours, as the authors evaluated the whole ICU stay whereas we assessed ICU stay up to obtaining the first positive sample, with a median of 14 days. This difference is of increasing relevance as it may be useful for future studies

on pre-emptive therapy. Malignancies have been strongly associated with candidemia development (17,21,23,26,27,34,35). In Latin America, Quindos et al. (7) supported this finding and reported a high frequency of *C. tropicalis* isolation in these patients, particularly in Brazil and Colombia, similar to our findings. Noteworthy, in our study, *C. krusei* was rather frequent among this population, which may be related to a frequent use of fluconazole in oncology wards that may select this species (25). Further, several studies have reported that more than 30% of cases present prior use of antibiotics, surgical interventions, corticosteroids, mechanical ventilation or parenteral nutrition (18,21,30). Noteworthy, our findings revealed a higher use of antibiotics and surgical interventions. Renal failure, chemotherapy, neutropenia or prior antifungal therapy are described in fewer studies (25,36,37,38). Regarding HIV status, an Australian study (34) reported less than 1% of patients positive to HIV, in contrast to Kreusch et al. (39) in South Africa, who reported up to 20%, which is probably due to a higher local prevalence of HIV infection (40). Our findings appear to be located in between, although every HIV positive patient had one or more additional risk factors for candidemia. Despite none of the assessed clinical features suggested an association with NCA species candidemia, a previous study in Taiwan described a higher frequency of neutropenia in patients with NCA species candidemia and a lower occurrence of candiduria and ICU stay, when compared to *C. albicans* candidemia (18).

A reduced sample of susceptibility tests was available. Most isolations were multi-sensible, although nearly 30% presented resistance to at least one antifungal agent, including one *C. krusei* isolate resistant to fluconazole, which is considered natural resistance. No resistance to amphotericin or echinocandins was observed. Despite a rather small sample, a high frequency of resistant isolates was observed. However, we do not rule out biased results, as available susceptibility tests may have been requested on a 'no response to first-line antifungal therapy' basis or in suspected resistance due to previous antifungal therapy. A local epidemiological study in our country (6) reported fluconazole resistance in up to 3% of isolations using the cut-off points of Clinical and Laboratory Standards Institute (CLSI) 2008, which increased to 20% using CLSI 2012 cut-off points. Similar results were concluded in a regional study with data from Colombia, Ecuador and Venezuela, which reported a 7% resistance to fluconazole (41). Worldwide studies have reported susceptibility to fluconazole in more than 90% of isolations (22,42,43).

Several clinical factors included in our study have been suggested as risk factors for candidemia development, although none was associated with an increased risk for NCA species infections. Due to the observed high frequency of prior antibiotic use and surgical interventions, we hypothesize that the alteration of the microbiota in the gastrointestinal tract may generate intestinal dysbiosis that allows fungal structures, such as *Candida* species, to thrive freely, colonize and ultimately disseminate (44,45). Immunocompromised patients (e.g., diabetes,

malignancies, immunosuppressed, renal failure) may be more prone to yeast invasive infections (45,46). New factors associated with the onset of candidemia, such as colonization by carbapenemase-producing *Klebsiella pneumoniae* and *Clostridium difficile* infections may support this hypothesis (47,48,49).

We acknowledge some drawbacks of our study. First, the small sample size may limit our results. Second, our institution is a national-renowned third-level hospital in which complex patients are usually treated, thus our data may reflect a selection bias. Third, due to the retrospective cross-sectional nature of our study, the identification of associations is limited, which may explain the absence of associations with clinical features. This fact supports the importance of case-control, multicenter and prospective studies that may allow the identification of relevant characteristics associated with NCA species infection. Although blood cultures are the current gold standard for candidemia diagnosis, their performance appears to be low. New diagnostic tests may improve diagnostic performance, particularly in invasive candidiasis cases (50,51).

Finally, new emerging *Candida* species with an antimicrobial resistant phenotype have been identified. One of such species is *C. auris*, which has been reported in over a dozen of countries, including our institution (33,52,53,54). Although this species was not observed in our study, an increasing awareness is warranted. *C. auris* should be suspected when species identification cannot be obtained or certain *Candida* species are identified (e.g., Rhodotorula glutinis, *C. famata, C. catenulate, C. haemulonii, C. sake*), particularly when standard biochemical identification kits are used (55).

Conclusion

Candida spp. is among the top five causes of bloodstream invasive infection worldwide, with a mortality rate of up to 60%. Our results support a shift towards NCA species infections, although no clinical variables were particularly associated. The identification of risk factors, earlier and timely diagnostic approaches and the improvement of prediction scores must be prioritized, in order to identify patients at high risk who may benefit from pre-emptive therapy.

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Additional information

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