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Candidemia in a Portuguese tertiary care hospital: Analysis of a 2-year period

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Candidemia in a Portuguese tertiary care hospital: Analysis of a 2-year period

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Ciências médicas e da saúde

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Candidemia in a Portuguese tertiary care hospital: Analysis of a 2-year period

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Candidemia in a Portuguese tertiary care hospital: Analysis of a 2-year period

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Abstract

Background: Candidemia is a nosocomial infection of increasing importance, associated with high morbidity and mortality. The aim of this study is to describe the species distribution, risk factors, management and outcomes of patients with candidemia.

Methods: We conducted a retrospective study at Centro Hospitalar Universitário de São João, Portugal, between January 2016 and December 2017.

Results: A total of 117 candidemia episodes (n=114 patients) were included. Median age was 65 years, with an increased prevalence of older ages. *Candida albicans* (51.3%) was the most prevalent species, followed by *C. glabrata* (22.2%), *C. parapsilosis* (15.4%), *C. tropicalis* (4.3%) and *C. lusitaniae* (2.6%). Forty-two patients (35.9%) did not receive antifungal drugs after diagnosis of candidemia. Echinocandins were used as first-line drug therapy in half of the treated patients (50.7%). The median EQUAL Candida Score was 6/17 (IQR 6-9) for patients without central venous catheter (CVC) and 11/20 (IQR 6-14) for patients with CVC. The 30 days-mortality was 31,6% and was not significantly associated with the timing of antifungal therapy and the EQUAL Candida Score.

Conclusion: The distribution of Candida species has changed in recent years, with an increase in the proportion of *C. albicans* and *C. glabrata*. Rapid diagnostic tests, empiric antifungal therapy and source control are essential to improve the prognosis of patients with candidemia. More multicentric prospective studies are needed to evaluate the association of mortality with the timing of antifungal therapy or the EQUAL Candida Score.

Keywords

Candida species

Candidemia

EQUAL Candida Score

Abbreviations: Invasive candidiasis (IC), Central venous catheter (CVC), Infectious Diseases Society of America (IDSA), European Society for Clinical Microbiology and Infectious Diseases (ESCMID), Intensive care units (ICU)

Introduction

Candida species are frequent colonizers of skin, gastrointestinal and genitourinary tracts. They may cause invasive disease when there is a compromise of the host defence mechanisms and/or rupture of anatomical barriers.

The most common form of invasive candidiasis (IC) is candidemia, defined as the presence of Candida species in the bloodstream. Positive blood culture for Candida should never be considered a contaminant and always needs further investigation [1].

Candida is the fourth most frequent cause of bloodstream infections in the United States and the seventh in Europe [2, 3]. The incidence of candidemia has increased over time and is associated with high mortality rates, prolonged hospital stays and high economic costs [4].

From the 15 Candida species that can cause disease in humans, five (*C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. krusei*) are responsible for 92% of candidemia cases [5]. The species distribution has changed over the last few decades. Although *C. albicans* continues to be the most frequent pathogen, its incidence is decreasing in comparison to non-albicans species, with *C. glabrata* assuming an increasingly relevant role in northern Europe, United States and Canada, and *C. parapsilosis* in southern Europe, Asia and South America [2, 5].

The most common risk factors for candidemia include immunosuppression, exposure to broad-spectrum antibiotics, the presence of central venous catheter (CVC), recent major surgery, necrotizing pancreatitis, total parenteral nutrition, diabetes mellitus, renal insufficiency, haemodialysis, mechanical ventilation, and candida colonization [1].

Correct management of candidemia is crucial for the patients' prognosis. Both the Infectious Diseases Society of America (IDSA) and European Society for Clinical Microbiology and Infectious Diseases (ESCMID) recommend as an initial antifungal agent an echinocandin, with treatment duration of 14 days after the first negative blood culture [6, 7]. Follow-up blood culture (at least one per day until negative), a fundoscopy to exclude occult ocular involvement and CVC removal as soon as possible in all patients is also recommended by these two societies [6, 7]. ESCMID additionally recommends the performing of transoesophageal echocardiography to detect cardiac valvular involvement [7]. EQUAL Candida Score is a tool developed to measure adherence to the strongest recommendations of the IDSA and ESCMID guidelines regarding diagnosis, follow-up and treatment of candidemia [8]. The maximum score is 20 points for CVC carriers and 17 points for non-CVC carriers [8]. The correlation between this score and the outcome is still under study [8].

Resistance to antifungal agents by Candida species is an emerging problem, with fluconazole resistance ranging from 0 to 5% in *C. albicans* and from 5 to 65% in non-albicans species [9]. Echinocandins resistance has been reported mostly for *C. glabrata*, where it ranges between 2 and 12% [10, 11].

The aim of this study is to describe the species distribution, risk factors, management and outcomes of patients with candidemia diagnosed at our hospital, over a 2-year period.

Materials and Methods

In this retrospective study, we included all patients from Centro Hospitalar Universitário de São João, Portugal, with at least one blood culture positive for Candida species between January 2016 and December 2017.

Candida-positive blood cultures of a single patient separated by a negative blood culture for Candida or subsequent positive blood cultures for two different Candida species were defined as a new episode. Candida species were identified by the hospital's Microbiology laboratory, using its routine method (MALDI-TOF from bioMérieux, VITEK® MS).

For each patient, the following variables were collected through clinical records: age, gender, hospital department at the time of the first positive blood culture, length of hospitalisation, risk factors (diabetes mellitus, CVC, total parenteral nutrition, previous antibacterial or antifungal therapy, necrotizing pancreatitis, mechanical ventilation, prostheses, chronic kidney disease, haemodialysis, previous surgery, gastrointestinal perforation, solid cancer, haematological malignancies, solid organ transplantation, bone marrow transplantation, HIV infection, chemotherapy, previous corticosteroid therapy and previous Candida colonization), species identification, antifungal susceptibility testing, antifungal therapy after diagnosis of candidemia, follow-up blood cultures, CVC removal, funduscopic examination, echocardiography, EQUAL Candida score, death and sequels. Death associated with candidemia was defined as death within 30 days after the first positive blood culture for Candida.

The antifungal susceptibility test is not routinely done and is only performed for exceptional clinical circumstances in an external laboratory. This variable was only collected when it was documented in clinical records.

Continuous data are expressed according to the variables' distribution [mean and standard deviation (SD) for normally distributed variables, and median and interquartile range (IQR) for non-normal distributed variables] and categorical data as proportions or percentages. We used the most suitable statistical test according to the variables' distribution. Statistical analysis was performed using SPSS 25.0 (IBM SPSS Statistics, IBM Corporation, Chicago, IL, USA). A p-value below 0.05 was considered significant.

This study was approved by the Ethics Committee for Health of the Centro Hospitalar Universitário de São João/Faculty of Medicine of the University of Porto.

Results

During the 2-year period of this study, 117 episodes of candidemia were reported from 114 patients. Two patients had two episodes of candidemia caused by different species of Candida and one patient had two episodes of candidemia by the same Candida species separated by negative blood culture.

The mortality, demographic and clinical characteristics of the study population are summarized in Table 1.

The median age was 65 years (IQR 48-75 years), with an increased prevalence for older ages. *C. albicans* was the most frequent species in older patients and *C. parapsilosis* in paediatric patients, accounting for 50% of the isolates in this age group. Fifty-nine (50.4%) candidemia episodes occurred in women and fifty-eight (49.6%) in men.

At the time of the first positive blood culture, 42.3% of the patients were in intensive care units (ICU) (29.8% in ICU level 3 and 12.5% in ICU level 2), 31.7% in surgical wards and 26.0% in medical wards.

The most common risk factors were previous antibacterial therapy (90.5%), the presence of CVC (74.3%), recent surgery (60.9%), previous corticosteroid therapy (40.5%), mechanical ventilation (36.8%) and solid cancer (29.3%). However, most patients have several risk factors for candidemia with a median of 6 risk factors by patient (IQR 4-13).

The median duration of hospitalization was 40 days (26-84 days). The period between hospital admission and Candida isolation in blood culture was in median 17 days (8-32 days). In 2 patients other forms of IC were identified after the diagnosis of candidemia (endocarditis and osteomyelitis, respectively).

C. albicans (51.3%) was the most frequently isolated species, followed by *C. glabrata* (22.2%), C. *parapsilosis* (15.4%), *C. tropicalis* (4.3%) and *C. lusitaniae* (2.6%). *C. krusei*, *C. guilliermondii*, C. sphaerica, *C. pelliculosa* and *C. rugosa* were isolated only in one patient each.

Patients with *C. glabrata* were less commonly exposed to previous antibiotic therapy (p = 0.001), and gastrointestinal perforation was less frequently associated with *C. albicans* (p = 0.003). Others species were significantly associated with haematological malignancies (p = 0.002) and bone marrow transplantation (p < 0.001).

The antifungal susceptibility testing was performed only for 2 episodes of candidemia, where a *C. parapsilosis* with intermediate sensitivity for fluconazole and resistant to echinocandins and a multisensible *C. albicans* were isolated. Ophthalmoscopy was performed in 35.0%, transthoracic echocardiography in 42.3% and transesophageal echocardiography in 9.3% of patients.

Forty-two patients (35.9%) did not receive antifungal drugs. The median time between blood culture collection and the patient's death was 2 days (IQR 1-5 days) for patients who did not receive treatment and 19 days (IQR 10-37 days) for those who underwent the treatment. Echinocandins were used as first-line drug therapy in the majority of patients (50.7%), followed by fluconazole (34.7%) and amphotericin B (13.3%).

Step-down to fluconazole occurred in 31.6% of patients who received an echinocandin as first-line drug therapy. The median duration of antifungal treatment was 17 days (IQR 8-23 days), with a median duration of antifungal treatment after the first negative blood culture of 15 days (IQR 8-22 days). The median time between blood culture collection and the start of antifungal therapy was 2 days (IQR 1-4 days) and was not significantly associated with mortality.

The CVC was removed after the diagnosis of candidemia in 80.0% of patients, in which 17.9% presented a CVC-tip culture positive for Candida.

The median EQUAL Candida Score was 6 (IQR 6-9) out of 17 for patients without CVC, and 11 (IQR 6-14) out of 20 for patients with CVC. Follow-up blood cultures were performed in 82.1% of the patients, however only in a minority of patients were collected daily. No statistically significant association was found between EQUAL Candida Score and mortality.

The 30 days-mortality was 31,6% and does not vary significantly between Candida species. The species that presented lower mortality were *C. glabrata* and *C. parapsilosis*, and the highest were less frequent non-albicans species.

Discussion

Candidemia remains a major challenge for health care, with an increasing incidence, despite the implementation of preventive strategies, due to the complexity of patients and advances in medical procedures [5, 12]. It has different epidemiologic patterns, according to the location and time period of the study [2, 5]. Thus, species distribution, susceptibility to antifungals, risk factors and outcomes should be analysed continuously.

This 2-year-retrospective study showed that *C. albicans* was the most frequently isolated species with a higher candidemia prevalence in older ages. Echinocandins were the first-line drug therapy in half of the treated patients, but about one-third of the patients never began antifungal therapy. Mortality was 31.6% and no correlation was found with time between Candida isolation in blood culture and the start of antifungal therapy or EQUAL Candida Score.

Median age, risk factors and comorbidities present in our population are similar to those most cited in the published literature [1, 2, 4, 13-15]. Compared to previous national data, we had a higher proportion of elderly and a lower proportion of newborns and children [16, 17]. Similar to others, most of the patients were hospitalized in ICU [15-18] and, although published data shows an increasing incidence of candidemia in medical wards [19], we found a higher proportion of surgical patients.

The widespread use of prophylaxis with fluconazole is one of the main factors responsible for the decrease in the incidence of *C. albicans* infections compared to non-albicans species [4]. In our study, *C. albicans* was the most frequently isolated species. However, and contrary to what would be expected, its prevalence increased over time compared to the other national studies (51.3% in 2016/2017 versus 40.4% in 2011/2012 and 35% in 2004) [16, 17]. Despite this, its frequency, of approximately 50%, is similar to the data that is found in the literature [15, 18, 20].

Another curious finding of our study is that the second most frequently isolated species was *C. glabrata*, presenting a higher prevalence than *C. parapsilosis*. In the literature, it is described that the frequency of these species varies according to the geographic area and age group, with *C. glabrata* being more frequent in Northern Europe and older ages, and *C. parapsilosis* in Southern Europe and paediatric ages [2, 4, 5]. On that account, an older population may be the reason for the higher rate of *C. glabrata* found by us.

Regarding the diagnosis, in our study, all cases were identified to species level. However, the antifungal susceptibility testing was performed only for 2 candidemia episodes, while in the other studies it is done routinely to all isolates [21-23]. Resistance to antifungal drugs has been increasing and therefore it is of utmost importance to know the local antifungal susceptibility of Candida species in order to adjust the empirical therapy, particularly now that fluconazole resistance can reach 50% in non-albicans infections [24]. Ocular involvement and infectious endocarditis can occur respectively in 16% [25] and 8.3% [26] of patients with candidemia, so ophthalmological examination and echocardiography are recommended by ESCMID and IDSA [6, 7]. The rates of these examinations in our study are still below the desired values.

CVC removal, which is associated with a reduction in candidemia mortality in some retrospective studies [22], was achieved in a satisfactory percentage of 80.0% of patients. On the contrary, although follow-up blood cultures were performed in most patients, only a small part satisfied the IDSA and ESCMID guidelines, one of the main aspects to be improved in the future.

Regarding treatment, 35.9% of the patients did not receive any antifungal drug, which is higher than what is described in other studies [21-23]. However, when we analysed the median time from blood culture collection to patient's death, we found that for patients who did not receive treatment the median was 2 days, while for those who underwent the treatment was 19 days. Thus, we can conclude that most of the patients died before the blood culture result was positive. This finding highlights the crucial role of early antifungal treatment and faster diagnostic methods to the improvement of candidemia prognosis. There is scientific evidence suggesting that empiric and pre-emptive antifungal therapy, based on symptoms or biomarkers, is associated with reduced mortality in patients with IC [27]. Blood cultures remain the gold standard for the diagnosis of IC. However, they only have a sensitivity of approximately 50%, with a median time to positivity of 2-3 days, which can reach 8 days in some cases [28]. Therefore, the use of rapid diagnostic tests is essential in these situations in order not to delay the initiation of treatment, which may jeopardize patient survival.

Echinocandins are recommended as the first-line drug [6, 7]. However, they were used in only half of the patients, with a considerable proportion of patients receiving fluconazole. According to the ESCMID and IDSA guidelines, step-down to fluconazole, which occurred in 31.6% of our patients, should be done if the patient is stable, tolerates the oral route and if the species is susceptible, which is not routinely assessed in our hospital as previously mentioned [6, 7].

The 30 days-mortality is within the expected range, around 30-40% [12]. The species that presented lower mortality were *C. glabrata* and *C. parapsilosis*, a finding also described by *Hii et al* [18, 29]. Less frequent non-albicans *Candida* species, as expected, showed the highest mortality [2, 13, 18, 29].

We did not find a correlation between time from blood culture collection to the start of antifungal therapy and mortality. It is undeniable that patients receiving adequate antifungal therapy have a better outcome. However, contradictory results have been published in relation to timing of antifungal therapy [12, 30]. As in our survey, EUROBACT study, a prospective multicenter cohort involving 1,156 ICU patients from 24 countries, failed to find an association between timing of antifungal therapy and mortality. One of the confounding effects pointed out by this study, that may explain this result, is that patients who initiate antifungal therapy earlier tend to be more critically ill with a higher risk of death [30]. Since our study is retrospective and involves non-ICU patients, other factors difficult to analyse may be at the origin of this finding, such as the severity of the acute illness, the comorbidities and the source control, all with impact in mortality.

As we can see from the EQUAL Candida Score medians, there is still a long way to achieve satisfactory ESCMID and IDSA guidelines adherence. Our study failed to show an association between this score and mortality. Several reasons related to study design may explain this finding. Additionally, in patients with a greater number of comorbidities, the benefit of guideline adherence may be masked by underlying diseases, which may be the main factor contributing to mortality. Thus, it is important to carry out more studies with a larger number of patients to investigate the existence or not of these associations.

This study has several limitations that have to be considered when interpreting the data. It is a retrospective single-centre study with a small and heterogeneous sample. Another of its limitations is the absence of the antifungal susceptibility testing for most cases, which makes it impossible to draw conclusions about antifungal resistance.

In conclusion, candidemia is a nosocomial infection of increasing importance, associated with high morbidity and mortality. The distribution of isolated Candida species in our hospital has changed in recent years, with an increase in the proportion of *C. albicans* and *C. glabrata*. In order to improve patient prognosis, it is fundamental to focus on the prevention of infection, as well as on the rapid diagnosis, empiric therapy and source control, managing the patients according to the best scientific evidence, in particular by guidelines adherence.

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Table 1: Mortality, distribution of demographics and clinical features by Candida species

	C. albicans (%) n=60	*C. glabrata* (%) n=26	*C. parapsilosis* (%) n=18	Others species* (%) n=13	Total n=117	*p*-value
Median age (years)	67	65	60	61	65	0.847
Age group						
≤15 years	3 (5.0%)	0	4 (22.2%)	1 (7.7%)	8 (6.8%)	0.170
16–59 years	20 (33.3%)	10 (38.5%)	5 (27.8%)	4 (30.8%)	39 (33.3%)	
≥60 years	37 (61,7%)	16 (61.5%)	9 (50.0%)	8 (61.5%)	70 (59.8%)	
Gender						
Female	26 (43.3%)	15 (57.7%)	11 (61.1%)	7 (53.8%)	59 (50.4%)	0.451
Male	34 (56.7%)	11 (42.3%)	7 (38.9%)	6 (46.2%)	58 (49.6%)	
Hospital department						
Medical wards	10 (18.5%)	8 (33.3%)	7 (46.7%)	2 (18.2%)	27 (26.0%)	0.289
Surgical wards	21 (38.9%)	4 (16.7%)	4 (26.7%)	4 (36.4%)	33 (31.7%)	
Intensive care unit level 2	9 (16.7%)	2 (8.3%)	1 (6.7%)	1 (9.1%)	13 (12.5%)	
Intensive care unit level 3	14 (25.9%)	10 (41.7%)	3 (20.0%)	4 (36.4%)	31 (29.8%)	
Median length of hospitalisation (days)	46	26	67	38	40	
Risk factos						
Diabetes mellitus	11 (18.6%)	9 (34.6%)	2 (11.1%)	4 (33.3%)	26 (22.6%)	0.185
Central venous catheter	40 (75.5%)	16 (66.7%)	11 (68.8%)	11 (91.7%)	78 (74.3%)	0.404
Total parenteral nutrition	15 (25.0%)	6 (23.1%)	8 (44.4%)	4 (30.8%)	33 (28.2%)	0.512
Antibacterial therapy**	57 (95.0%)	**19 (73.1%)*** **	16 (94.1%)	13 (100.0%)	105 (90.5%)	**0,007*** **
Antifungal therapy**	9 (15.0%)	6 (23.1%)	6 (35.3%)	4 (30.8%)	25 (21.6%)	0.250
Necrotizing pancreatitis**	1 (1.7%)	0	2 (11.1%)	1 (7.7%)	4 (3.4%)	0.143
Mechanical ventilation	17 (33.3%)	9 (34.6%)	7 (41.2%)	6 (50.0%)	39 (36.8%)	0.716
Prostheses	16 (27.6%)	5 (19.2%)	5 (29.4%)	2 (16.7%)	28 (24.8%)	0.731
Chronic kidney disease	12 (21.1%)	4 (15.4%)	1 (5.9%)	1 (7.7%)	18 (15.9%)	0.382
Haemodialysis	8 (16.0%)	1 (3.8%)	4 (25.0%)	3 (23.1%)	16 (15.2%)	0.218
Previous surgery**	38 (63.3%)	15 (57.7%)	11 (61.1%)	6 (54.5%)	70 (60.9%)	0.930
Gastrointestinal perforation**	**3 (5.1%)*** **	7 (26.9%)	5 (27.8%)	2 (16.7%)	17 (14.8%)	**0.019*** **
Solid cancer	18 (30.0%)	8 (30.8%)	5 (27.8%)	3 (25.0%)	34 (29.3%)	0.983
Haematological malignancies	4 (6.7%)	4 (15.4%)	1 (5.6%)	**5 (38.5%)*** **	14 (12.0%)	**0.010*** **
Solid organ transplantation	1 (1.7%)	2 (7.7%)	1 (5.6%)	1 (8.3%)	5 (4.3%)	0.517
Bone marrow transplantation	1 (1.7%)	0	0	**3 (25.0%)*** **	4 (3.4%)	**<0.001*** **
HIV infection	2 (3.3%)	1 (3.8%)	1 (5.6%)	0	4 (3.4%)	0.591
Chemotherapy**	7 (11.9%)	5 (20.0%)	2 (11.1%)	4 (33.3%)	18 (15.8%)	0.252
Corticosteroid therapy**	25 (43.9%)	8 (32.0%)	4 (25.0%)	8 (61.5%)	45 (40.5%)	0.172
Candida colonization**	16 (28.6%)	5 (19.2%)	1 (5,9%)	4 (30.8%)	26 (23.2%)	0.220
30 days-mortality (%)	19 (31.7%)	6 (23.1%)	4 (22.2%)	8 (61.5%)	37 (31.6%)	0.072

*Including *C. tropicalis* (n=5), *C. lusitaniae* (n=3), *C. krusei* (n=1), *C. guilliermondii* (n=1), *C. sphaerica* (n=1), *C. pelliculosa* (n=1) and *C. rugosa* (n=1) **60 days before the first positive blood culture ***When *p*-value reaches significance, the data appears in bold

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Anexos

Anexo I − Normas de Publicação da Revista “Journal of Medical Mycology”

Anexo II – Parecer da Comissão de Ética para a Saúde do Centro Hospitalar de São João/Faculdade de Medicina da Universidade do Porto

JOURNAL DE MYCOLOGIE MÉDICALE

Journal of Medical Mycology

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• Number the illustrations according to their sequence in the text.
• Use a logical naming convention for your artwork files.
• Provide captions to illustrations separately.
• Size the illustrations close to the desired dimensions of the published version.
• Submit each illustration as a separate file.
A detailed guide on electronic artwork is available.
You are urged to visit this site; some excerpts from the detailed information are given here.
Formats
If your electronic artwork is created in a Microsoft Office application (Word, PowerPoint, Excel) then please supply 'as is' in the native document format.
Regardless of the application used other than Microsoft Office, when your electronic artwork is finalized, please 'Save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):
EPS (or PDF): Vector drawings, embed all used fonts.
TIFF (or JPEG): Color or grayscale photographs (halftones), keep to a minimum of 300 dpi.
TIFF (or JPEG): Bitmapped (pure black & white pixels) line drawings, keep to a minimum of 1000 dpi.
TIFF (or JPEG): Combinations bitmapped line/half-tone (color or grayscale), keep to a minimum of 500 dpi.
Please do not:
• Supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); these typically have a low number of pixels and limited set of colors;
• Supply files that are too low in resolution;
• Submit graphics that are disproportionately large for the content.

Color artwork
Please make sure that artwork files are in an acceptable format (TIFF (or JPEG), EPS (or PDF) or MS Office files) and with the correct resolution. If, together with your accepted article, you submit usable color figures then Elsevier will ensure, at no additional charge, that these figures will appear in color online (e.g., ScienceDirect and other sites) in addition to color reproduction in print. Further information on the preparation of electronic artwork.

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Figure captions
Ensure that each illustration has a caption. Supply captions separately, not attached to the figure. A caption should comprise a brief title (**not** on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

Tables

Please submit tables as editable text and not as images. Tables can be placed either next to the relevant text in the article, or on separate page(s) at the end. Number tables consecutively in accordance with their appearance in the text and place any table notes below the table body. Be sparing in the use of tables and ensure that the data presented in them do not duplicate results described elsewhere in the article. Please avoid using vertical rules and shading in table cells.

References

Citation in text
Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication.

Reference links
Increased discoverability of research and high quality peer review are ensured by online links to the sources cited. In order to allow us to create links to abstracting and indexing services, such as Scopus, CrossRef and PubMed, please ensure that data provided in the references are correct. Please note that incorrect surnames, journal/book titles, publication year and pagination may prevent link creation. When copying references, please be careful as they may already contain errors. Use of the DOI is highly encouraged.

A DOI is guaranteed never to change, so you can use it as a permanent link to any electronic article. An example of a citation using DOI for an article not yet in an issue is: VanDecar J.C., Russo R.M., James D.E., Ambeh W.B., Franke M. (2003). Aseismic continuation of the Lesser Antilles slab beneath northeastern Venezuela. Journal of Geophysical Research, https://doi.org/10.1029/2001JB000884. Please note the format of such citations should be in the same style as all other references in the paper.

Web references
As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

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References in a special issue
Please ensure that the words 'this issue' are added to any references in the list (and any citations in the text) to other articles in the same Special Issue.

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http://open.mendeley.com/use-citation-style/journal-de-mycologie-medicale
When preparing your manuscript, you will then be able to select this style using the Mendeley plug-ins for Microsoft Word or LibreOffice.

Reference style
Text: Indicate references by number(s) in square brackets in line with the text. The actual authors can be referred to, but the reference number(s) must always be given.
List: Number the references (numbers in square brackets) in the list in the order in which they appear in the text.
Examples:
Reference to a journal publication:
[1] Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. J Sci Commun 2010;163:51–9. https://doi.org/10.1016/j.Sc.2010.00372.
Reference to a journal publication with an article number:
[2] Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. Heliyon. 2018;19:e00205. https://doi.org/10.1016/j.heliyon.2018.e00205
Reference to a book:
[3] Strunk Jr W, White EB. The elements of style. 4th ed. New York: Longman; 2000.
Reference to a chapter in an edited book:
[4] Mettam GR, Adams LB. How to prepare an electronic version of your article. In: Jones BS, Smith RZ, editors. Introduction to the electronic age, New York: E-Publishing Inc; 2009, p. 281–304.
Reference to a website:
[5] Cancer Research UK. Cancer statistics reports for the UK, http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/; 2003 [accessed 13 March 2003].
Reference to a dataset:
[dataset] [6] Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. https://doi.org/10.17632/xwj98nb39r.1.
Note shortened form for last page number. e.g., 51–9, and that for more than 6 authors the first 6 should be listed followed by 'et al.' For further details you are referred to 'Uniform Requirements for Manuscripts submitted to Biomedical Journals' (J Am Med Assoc 1997;277:927–34) (see also Samples of Formatted References).

Journal abbreviations source
Journal names should be abbreviated according to the List of Title Word Abbreviations.

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Supplementary material such as applications, images and sound clips, can be published with your article to enhance it. Submitted supplementary items are published exactly as they are received (Excel or PowerPoint files will appear as such online). Please submit your material together with the article and supply a concise, descriptive caption for each supplementary file. If you wish to make changes to supplementary material during any stage of the process, please make sure to provide an updated file. Do not annotate any corrections on a previous version. Please switch off the 'Track Changes' option in Microsoft Office files as these will appear in the published version.

AFTER ACCEPTANCE

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Unidade de Investigação

Tomei conhecimento. Nada a opor.

03 de Janeiro de 2019

A Coordenadora da Unidade de Investigação

(Prof.ª Doutora Ana Azevedo)

n.º 369/18

SÃO JOÃO

DIRECÇÃO CLÍNICA

Aprovado. Ao CA. 4 01 2019

(Prof.ª Doutora Ana Azevedo)

PEDIDO DE AUTORIZAÇÃO

Realização de Investigação

Exmo. Senhor Presidente do Conselho de Administração do Centro Hospitalar de São João

AUTORIZADO

CONSELHO DE ADMINISTRAÇÃO REUNIÃO DE 09 JAN 2019

Presidente do Conselho de Administração

(Dr. António Oliveira e Silva)

Diretor Clínico | Enfermeira Diretora | Vogal Executivo | Vogal Executivo

(Dr. José Artur Paiva) | (Enf.ª Filomena Cardoso) | (Dr. Luís Porto Gomes) | (Dr. Renato G. Matos)

Nome do Investigador Principal:

Sara Inês Pinto Magalhães

Título da Investigação:

Candidemias no Centro Hospitalar Universitário de São João – Avaliação Retrospetiva nos Últimos 10 Anos

Pretendendo realizar no(s) Serviço(s) de:

Doenças Infecciosas

a investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efetivação.

Para o efeito, anexo toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de São João/ Faculdade de Medicina da Universidade do Porto respeitante à investigação, à qual enderecei pedido de apreciação e parecer.

Com os melhores cumprimentos.

O Investigador/ Promotor

Porto, 26 *de* Novembro *de* 2018 . Sara Magalhães

assinatura

Centro Hospitalar São João

Centro de Epidemiologia Hospitalar

26/12/2018

CES-IM005-0

Parecer da Comissão de Ética para a Saúde do
Centro Hospitalar Universitário de São João / Faculdade de Medicina da Universidade do Porto

Título do Projecto: Candidemias no CHUSJ - avaliação retrospectiva nos últimos 10 anos

Nome da Investigadora Principal: Sara Inês Pinto Magalhães, aluna do Mestrado Integrado em Medicina da FMUP

Onde decorre o Estudo: No Serviço de Doenças Infecciosas. Dispõe de autorização do Prof. Doutor António Sarmento. Irá ter como profissional de ligação a Prof.ª Doutora Maria Lurdes Campos Santos, que também é a orientadora.

Objectivos do Estudo:
Este trabalho de investigação tem como principal objectivo descrever a epidemiologia das candidemias no CHUSJ e comparar com estudos anteriores. Avaliar a qualidade da abordagem inicial, utilização de antifúngicos e adesão às recomendações internacionais.

Estudo realizado no âmbito do Mestrado Integrado em Medicina da FMUP, sob orientação da Prof.ª Doutora Maria Lurdes Campos Santos.

Concepção e Pertinência do estudo:
Estudo observacional retrospectivo, descritivo, sem intervenção. Período de estudo: 2008-2017. Todos os doentes com candidemias identificadas pelo Laboratório de Microbiologia do CHUSJ.

Benefício/risco: Não aplicável

Confidencialidade dos dados:
A recolha, gestão, tratamento e apresentação dos dados não permitirá a identificação dos participantes no estudo, que serão identificados por um código numérico.

Respeito pela liberdade e autonomia do sujeito de ensaio: Não aplicável

***Curriculum* da investigadora**: Adequado à investigação.

Data previsível da conclusão do estudo: Março de 2019

Conclusão: Proponho um parecer favorável à realização deste projecto de investigação.

Porto, 14 de Dezembro de 2018

O Relator da CES,

SÃO JOÃO

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

Questionário para submissão de Investigação

Exmo. Sr. Presidente da Comissão de Ética do Centro Hospitalar de São João/ Faculdade de Medicina da Universidade do Porto,

Pretendendo realizar a investigação infracitada, solicito a V. Exa., na qualidade de Investigador, a sua apreciação e a elaboração do respetivo parecer. Para o efeito, anexo toda a documentação requerida.

IDENTIFICAÇÃO DO ESTUDO

Título da investigação: Candidemias no Centro Hospitalar Universitário de São João – Avaliação Retrospetiva nos Últimos 10 Anos

Nome do investigador: Sara Inês Pinto Magalhães

Endereço eletrónico: saraipmagalhaes94@gmail.com **Contacto telefónico:** 919377841

Caracterização da investigação:

☐ Estudo retrospetivo ☒ Estudo observacional ☐ Estudo prospetivo

☐ Inquérito ☐ Outro. Qual? _____

Tipo de investigação:

☐ Com intervenção ☒ Sem intervenção

Formação do investigador em boas práticas clínicas *(GCP)*: ☐ Sim ☒ Não

Promotor *(se aplicável)*: _____

Nome do orientador de dissertação/tese *(se aplicável)*: Professora Doutora Maria Lurdes Campos Santos

Endereço eletrónico: maria.lurdes.uci@gmail.com

Local/locais onde se realiza a investigação: Serviço de Doenças Infecciosas do Centro Hospitalar Universitário de São João

Data prevista para início: 17 / 12 / 2018 Data prevista para o término: 31 / 03 / 2019

PROTOCOLO DO ESTUDO

Síntese dos objetivos:

Descrever a epidemiologia das candidemias no Centro Hospitalar Universitário de São João (CHUSJ) e comparar com estudos anteriores já realizados neste hospital. Avaliar a qualidade da abordagem inicial, utilização de antifúngicos e adesão às recomendações internacionais

Fundamentação ética (ganhos em conhecimento/inovação; ponderação benefícios/riscos):

Candidemia é uma importante causa de morbidade e mortalidade, estando associada a hospitalizações prolongadas e custos económicos avultados. A sua incidência tem aumentado e a distribuição das espécies mudado ao longo das últimas décadas. A resistência aos antifúngicos é também um problema crescente. Assim, é fundamental conhecer a epidemiologia do CHUSJ de forma a otimizar o tratamento empírico e o prognóstico dos doentes com candidemia

CONFIDENCIALIDADE

De que forma é garantida a anonimização dos dados recolhidos de toda a informação?

A recolha, gestão, tratamento e apresentação dos dados não permitirá a identificação dos participantes no estudo, que serão identificados por um código numérico

O investigador necessita ter acesso a dados do processo clínico? ☒ Sim ☐ Não

Está previsto o registo de imagem ou som dos participantes? ☐ Sim ☒ Não

Se sim, está prevista a destruição deste registo após o sua utilização? ☐ Sim ☐ Não

CONSENTI MENTO

O estudo implica recrutamento de:

Doentes: ☒ Sim ☐ Não Voluntários saudáveis: ☐ Sim ☒ Não

Menores de 18 anos: ☒ Sim ☐ Não

Outras pessoas sem capacidade do exercício de autonomia: ☒ Sim ☐ Não

A investigação prevê a obtenção de Consentimento Informado: ☐ Sim ☒ Não

Se não, referir qual o fundamento para a isenção:

Estudo observacional descritivo sem intervenção

Existe informação escrita aos participantes: ☐ Sim ☒ Não

PROPRIEDADE DOS DADOS

A investigação e os seus resultados são propriedade intelectual de:

☐ Investigador ☐ Promotor ☐ Ambos ☒ Serviço onde é realizado

☐ Não aplicável Outro: _____

BENEFÍCIOS, RISCOS E CONTRAPARTIDAS PARA OS PARTICIPANTES

Benefícios previsíveis:

Contribuição para o conhecimento da questão em investigação

Riscos/incómodos previsíveis:

Sem risco ou incómodos previsíveis

São dadas contrapartidas aos participantes:

- *pela participação* ☐ Sim ☐ Não ☒ Não aplicável
- *pelas deslocações* ☐ Sim ☐ Não ☒ Não aplicável
- *pelas faltas ao emprego* ☐ Sim ☐ Não ☒ Não aplicável
- *por outras perdas e danos* ☐ Sim ☐ Não ☒ Não aplicável

CUSTOS / PLANO FINANCEIRO

Os custos da investigação são suportados por:

☐ Investigador ☐ Promotor ☐ Serviço onde é realizado

☒ Não aplicável Outro: _____

Existe protocolo financeiro? ☐ Sim ☒ Não

LISTA DE DOCUMENTOS ANEXOS

- [x] Pedido de autorização ao Presidente do Conselho de Administração do Centro Hospitalar de São João *(se aplicável)*
- [ ] Pedido de autorização à Diretora da Faculdade de Medicina da Universidade do Porto *(se aplicável)*
- [x] Protocolo do estudo
- [x] Declaração do Diretor de Serviço onde decorre o estudo

  (sendo um estudo na área de enfermagem deve anexar também a concordância da chefia de enfermagem)
- [x] Profissional de ligação
- [x] Informação dos orientadores
- [ ] Informação ao participante
- [ ] Modelo de consentimento
- [ ] Instrumentos a utilizar *(inquéritos, questionários,escalas, p.ex.)*: _____
- [x] Curriculum Vitae abreviado *(máx. 3 páginas)*
- [ ] Protocolo financeiro
- [x] Outros:

Pedido de reutilização de Registos Clínicos para Investigação e Desenvolvimento

COMPROMISSO DE HONRA E DECLARAÇÃO DE INTERESSES

Declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (1960 e respetivas emendas), e da Organização Mundial da Saúde, Convenção de Oviedo e das "Boas Práticas Clínicas" (GCP/ICH) no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo, nos últimos três meses. Comprometo-me a entregar à CES o relatório final da investigação, assim que concluído.

Porto, 26 *de* Novembro *de* 2018

Nome legível: Sara Inês Pinto Magalhães

Sara Magalhães
assinatura

Parecer da Comissão de Ética do Centro Hospitalar de São João/ FMUP Emitido na reunião plenária da CE de 14 / 12 / 18

A Comissão de Ética para a Saúde APROVA por unanimidade o parecer do Relator, pelo que nada tem a opor à realização deste projecto de investigação.

Prof. Doutor Filipe Almeida
Presidente da Comissão de Ética

369-18

RESPONSÁVEL PELO ACESSO À INFORMAÇÃO

SÃO JOÃO

Pedido de Reutilização de Registos Clínicos para Investigação e Desenvolvimento (I&D)

Número do Pedido
1|8|0|1|5|6|1|1|7
(A preencher pelo Gabinete de Apoio ao RAI)

Exmo. Senhor
Responsável pelo Acesso à Informação
(Artigo 9.º da Lei n.º 26/2016 de 22 de agosto)
Dr. Rui de Vasconcellos Guimarães

SÃO JOÃO
RAI - Responsável pelo Acesso à Informação - Centro Hospitalar de São João
(Art.º 9º, Lei 26/2016, de 22/8)
AUTORIZADO

1. Identificação do(s) Investigador(es) *Preenchimento Obrigatório*

1.1. Investigador Principal
Nome Sara Inês Pinto Magalhães
Contacto telefónico 9|1|9|3|7|7|8|4|1| | | | |
Endereço eletrónico saraipmagalhaes94 @ gmail.com

1.2. Investigador(es) Associado(s)
Número Total: 2
Nome Maria Lurdes Campos Santos
Contacto telefónico 9|6|2|8|3|5|5|0|3| | | | |
Endereço eletrónico maria.lurdes.uci @ gmail.com

Nome André da Silva Marques Pinto
Contacto telefónico 9|1|6|5|1|6|2|9|3| | | | |
Endereço eletrónico pintoandre @ gmail.com

Nome
Contacto telefónico | | | | | | | | | | | | | |
Endereço eletrónico @

1.3. Afiliação Institucional do Investigador Principal
1.3.1. Grupo Profissional
☐ Médico(a) ☐ Enfermeiro(a) ☐ Docente ☒ Estudante
☐ Outro. Qual?

1.3.2. Documento de identificação pessoal ou profissional
☒ Cartão de Cidadão ☐ Bilhete de Identidade ☐ Célula Profissional
☐ Cartão de Docente ☐ Cartão de Estudante ☐ Outro. Qual?
Número de Documento | | | | | | | | | | | | | |

2. Enquadramento e Identificação do Trabalho de Investigação e Desenvolvimento *Preenchimento Obrigatório*

2.1. Enquadramento da investigação
☒ Trabalho académico de investigação e desenvolvimento:
☐ Não conferidor de grau
☒ Conferidor de grau: ☐ Licenciatura ☒ Mestrado ☐ Doutoramento
☐ Projeto de investigação e desenvolvimento

RAI-IM002-0

2.2. Entidade(s) que tutela(m) a investigação

☒ Centro Hospitalar de São João

Serviço: Doenças Infecciosas

☒ Universidade do Porto

Faculdade / Instituto: Faculdade de Medicina da Universidade do Porto

☐ Outra Instituição. *Qual?*

Há alguma parceria entre instituições?

☒ Não ☐ Sim. Qual(is)?

2.3. Orientador *Se Aplicável*

Contacto telefónico 962835503

Endereço eletrónico maria.lurdes.uci @ gmail.com

2.4. Título provisório

Candidemias no Centro Hospitalar Universitário de São João – Avaliação Retrospetiva nos Últimos 10 Anos

Deverá posteriormente indicar o título definitivo para emissão do Certificado de Reutilização pelo RAI - DAta REuse Certificate for Research - DARE através dos contactos disponíveis no fim deste formulário.

2.5. Acesso requerido

☐ Ficheiro

Descrição do património informacional a que pretende ter acesso, identificando a informação a obter, i.e. nome, morada, diagnóstico, idade, códigos dos distritos, entre outros.

☒ Consulta de processos clínicos em ambiente papel:

☐ Bloco ☐ Consulta Externa ☐ Hospital de Dia ☒ Internamento ☒ MCDT ☒ Urgência

Deverá anexar ficheiro(s) contendo a identificação do pretendido, i.e. números de processos, episódios, números de utente, entre outros.

Anexar ficheiro no ato de envio

☒ Consulta de registos clínicos eletrónicos

Especificar os Sistemas de Informação:

SClínico, SAM

Data previsível de fim de utilização das credenciais de acesso 2019-03-31

☐ Outro Acesso. Qual?

2.3. Pareceres e Autorizações

☐ Autorização da Hierarquia

☐ Protocolo Científico Aprovado [1]

☒ Parecer da Comissão de Ética para a Saúde (CES) [1]

☐ Parecer do Centro de Epidemiologia Hospitalar [1]

Deverá anexar ficheiro(s) contendo cópia dos documentos referentes às opções selecionadas.

Anexar ficheiro no ato de envio

[1] *Obrigatório quando aplicável*

3. Observações *Preenchimento Facultativo*

4. Aceitação dos Termos e Condições da Reutilização

Cumulativamente com as obrigações decorrentes da lei já citada *(n.º 2 e 3 do artigo 21 e o n.º 1 e 2 do artigo 12, ambos da Lei n.º 26/2016, de 22 de agosto)* ao submeter o presente pedido concordo e fico ainda vinculado aos seguintes termos e condições:

- Comprometo-me a manter confidencial toda a informação à qual vou ter acesso;
- Não vou elaborar registos, susceptíveis de identificar ou tornar identificável a identidade das pessoas a quem os mesmos dizem respeito;
- Não vou elaborar, nem ficar na posse, de cópias de bases de dados utilizadas na recolha de informação;
- Comprometo-me a obter junto da Comissão Nacional de Proteção de Dados (CNPD) as necessárias autorizações, para eventuais bases de dados que venha a conceber e utilizar no âmbito da presente investigação;
- Comprometo-me a devolver ao Centro Hospitalar de São João, na pessoa do seu Diretor Clínico, as bases de dados e o resultado da investigação;
- Comprometo-me a ocultar os elementos de identificação da(s) pessoa(s) a quem os registos digam respeito, em futuras e eventuais publicações de resultados;
- Comprometo-me a consultar os processos clínicos nas instalações que me forem indicadas para o efeito;
- Comprometo-me a obter os necessários pareceres, quer da Comissão de Ética do Hospital, quer do Centro de Epidemiologia Hospitalar, sempre que necessário;
- Comprometo-me a citar as fontes sempre que publicitar o trabalho de investigação independentemente de requerer a Certidão de Reutilização (DAta REuse Certificate for Research – DARE);
- Tomei conhecimento, que a violação de qualquer dos compromissos aqui assumidos, resultará no apuramento de responsabilidades disciplinares, civis e penais e ainda, à impossibilidade futura de aceder a informação de saúde para fins de investigação.

5. Decisão do investigador sobre requerer a DAta REuse Certificate for Research – DARE *Preenchimento Obrigatório*

☒ Pretendo desde já requerer a Certidão de Reutilização (DARE) cujo sentido, valor e significado consultei em *http://portal-chsj.min-saude.pt/pages/710.*

☐ Não pretendo requerer a Certidão de Reutilização (DARE) cujo sentido, valor e significado consultei em *http://portal-chsj.min-saude.pt/pages/710.*

6. Assinatura

Nota 1: Se o presente pedido for submetido eletronicamente ou faz assinatura digital qualificada; ou posteriormente vem ao Centro Hospitalar de São João exibir o seu documento de identificação pessoal; ou no âmbito do seu espaço de liberdade e como manifestação expressa do seu consentimento envia cópia do referido documento, neste caso, concluído o processo ser-lhe-á devolvida ou eliminada a cópia do documento de identificação pessoal, conforme as indicações que dê.
Nota 2: Se o presente pedido for entregue presencialmente, assina e exibe o documento de identificação a quem recebe o pedido.

Data 2018-11-26

Sara Magalhães

Investigador Principal

Em caso de dúvida no preenchimento contacte através dos endereços eletrónicos
rai.reutilizacao.id@chsj.min-saude.pt **ou** ruiguimaraes@chsj.min-saude.pt
ou pelos números de telemóvel 962 204 194 **ou** 918 880 299

SUBMETER