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Unresolved issues in the diagnosis of catheter related candidemia: A position paper

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ABSTRACT

The incidence and recent trends of candidemia and the contribution of the COVID-19 pandemic to its evolution are not well documented. The catheter is a major focus of *Candida* spp. infections, but the methods used to confirm the origin of candidemia are still based on the data generated for bacterial infection. The presence of *Candida* spp. on the tip of a removed catheter is the gold standard for confirmation but it is not always possible to remove it. Conservative methods, without catheter removal, have not been specifically studied for microorganisms whose times of growth are different from those of bacteria and therefore these results are not applicable to candidemia. The different *Candida* species do not have a particular tropism for catheter colonization and fungal biomarkers have not yet been able to contribute to the determination of the origin of candidemia. Techniques such *Candida* T2 Magnetic Resonance (T2MR) has not yet been applied for this purpose. Finally, there is not yet a consensus of how to proceed when *Candida* spp. is isolated from an extracted catheter and blood cultures obtained from simultaneous peripheral veins are negative. In this lack of firm data, a group of experts has formulated a series of questions trying to answer them based on the literature, indicating the current deficiencies and offering their own opinion. All authors agree with the conclusions of the manuscript and offer it as a position and discussion paper.

Keywords: Catheter-Related Bloodstream Infections (CRBSI), catheter related candidemia (CRC), Candidemia, Catheter tip, Endovascular catheter.

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Cuestiones no resueltas en el diagnóstico de la candidemia relacionada con el catéter: un documento de opinión

RESUMEN

La incidencia y las tendencias recientes de la candidemia y la contribución de la pandemia de COVID-19 a su evolución no están bien documentadas. El catéter es uno de los principales focos de infecciones por *Candida* spp., pero los métodos empleados para confirmar el origen de la candidemia siguen basándose en los datos generados para la infección bacteriana. La presencia de *Candida* spp. en la punta de un catéter retirado es el método de referencia para la confirmación, pero no siempre es posible proceder a dicha retirada. Los métodos conservadores, sin retirada del catéter, no han sido estudiados específicamente para microorganismos cuyos tiempos de crecimiento son diferentes a los de las bacterias y, por tanto, estos resultados no son aplicables a la candidemia. Las diferentes especies de *Candida* spp. no tienen un tropismo particular para la colonización del catéter y los biomarcadores fúngicos, aún no han podido contribuir a la determinación del origen de la candidemia. Técnicas como la resonancia magnética T2MR todavía no se ha empleado para este fin. Por último, todavía no existe un consenso sobre cómo proceder cuando se aísla *Candida* spp. en un catéter extraído y los hemocultivos obtenidos por venas periféricas simultáneas son negativos. Ante esta falta de datos firmes, un grupo de expertos ha formulado una serie de preguntas y ha tratado de responderlas en base a la literatura, indicando las carencias presentes y ofreciendo su propia opinión. Todos los autores están de acuerdo con las conclusiones del manuscrito y lo ofrecen como documento de posición y discusión.

Palabras clave: Infecciones del torrente sanguíneo relacionadas con el catéter, candidemia relacionada con el catéter, candidemia, punta catéter, catéter endovascular.

INTRODUCTION

Candidemia is a major problem in today's hospitals. Its incidence and evolution is estimated to vary widely from one geographical area to another and the impact of the COVID-19 pandemic on the incidence of candidemia has not been sufficiently evaluated [1-3].

A high, but imprecise, percentage of candidemic episodes, have their origin in endovascular catheters, but their implication as a cause of candidemia is very difficult to prove, at least without proceeding to catheter removal, since none of the conservative procedures (without catheter removal) have demonstrated sufficient reliability [4-6]. Moreover, catheter removal in patients with candidemia, if performed systematically, often leads to the demonstration that the catheter or catheters were not the cause of the problem, with the implications that such a maneuver has for the patient's morbidity and for the economic budget. On the other hand, quantitative or semiquantitative methods to assess catheter tips colonizations have break points that have not been obtained specifically for *Candida* spp., but for bacterial infections.

The lack of scientific evidence on these aspects of candidemic episodes in patients with endovascular catheters has led us to ask a series of questions that we have submitted to a group of experts, both clinicians and microbiologists, in an attempt to obtain an opinion that may be useful to all those who daily face these problems.

The pertinent questions have been discussed and agreed upon by all the authors, trying to reach a position conclusion that could be useful for the readers. The questions and the author's positions on the different issues are included below.

WHAT IS THE INCIDENCE OF CANDIDEMIA AND ITS TREND IN RECENT YEARS, INCLUDING THE COVID-19 PANDEMIC?

Table 1 lists the few papers providing data on the incidence of candidemia published in the last 10 years. Obviously, the incidence of candidemia varies depending on factors such as geographic area, patient conditions, institution, and many other variables [7-9]. The few population-based studies yield very different figures. In the case of the United States of America, figures reported in 2015 ranged from 14 to 31 episodes/100,000 population [9]. However, the CDC reported in 2020 data from an active population-based surveillance for candidemia in 9 states, encompassing approximately 17 million persons. They estimated the incidence of candidemia in 7.0 cases per 100,000 inhabitants-year, with highest rates in adults aged ≥ 65 years (20.1/100,000).

Alternatively, European figures seem lower and data from Switzerland and Greece respectively reported incidences of 4.20 and 5.56 episodes per 100,000 inhabitants-year obtained in the last 10 years [8,10]. The calculated incidence in a health care area of the city of Madrid in the year 2021 was 5.76/100,000 inhabitants-year (Muñoz, P. et al. Unpublished information), in agreement with those mentioned in the old continent. Regarding Asia, data from Kuwait give a figure of 5.29 episodes per 100,000 inhabitants-year [11].

The incidence of candidemia has also been reported based on the denominator of 1,000 hospital admissions-year. Data were equally variable with figures ranging from 0.09 and 4.8 episodes in different countries [8,12]. The lowest incidence data range from 0.09 to 1.18 [8,13-15], intermediate data between 1.22-2.9 [16,17], reaching a maximum value of 4.8 [12,18]. The incidence of candidemia obtained in one of our institutions in Madrid in 2021 was 1.15 episodes/1,000 admissions-year (Muñoz, P. et al. Unpublished information).

Regarding the evolution of the figures in recent years, the review of the literature does not allow us to be conclusive in stating whether the incidence of candidemia has increased or decreased in the last decade. Several studies suggest an increase in the incidence of candidemia in European countries. In Switzerland, for example, an increase from 2.96 to 4.20 episodes/100,000 inhabitants-year is described [8]. In Italy, rises from 0.10 to 0.30 cases/1,000 patient-days [19,20] and the same is published from Ireland, Greece, France and Turkey [21-23]. Outside Europe, we have been able to find figures of increased incidence of candidemia in recent years in Brazil and Taiwan [3,12,24,25].

In contrast, there are publications of different geographic origin reporting declines in incidence over the last decade. Cleveland et al. [9] observed a significant decreasing trend in the cities of Atlanta and Baltimore between the years 2008 and 2013. For their part, Suzuki et al. [26] reach similar results, calculating that the incidence decreased steadily since 2004 in Veterans Administration hospitals in the USA.

Finally, data from Japan report stable candidemia numbers in recent years in a series of more than 55,000 cases but without precise population data [27] and the same occurs elsewhere [28,29].

On the other hand, the impact of the COVID-19 pandemic on the incidence of candidemia is summarized in Table 2. The few reported studies have been performed on the denominator of hospital admissions. Nucci et al. from Brazil report an overall increase in the incidence of candidemia from 1.54 per 1,000 admissions-year in the pre-pandemic period to 7.44 episodes per 1,000 admissions-year in patients with COVID-19 [12] versus 4.76 per 1,000 patients-year admitted with non-COVID-19 conditions during the pandemic period. In Italy, Mastrangelo et al. report incidences of 1.1 versus 0.15/1,000 admissions-year in cases with and without COVID-19 [30]. Data from one of our institutions show an incidence of 4.73 versus 0.85 episodes per 1,000 admissions-year in patients with and without COVID-19 respectively [31]. There is even less information on the origin of candidemia in patients with COVID-19. The study by Pérez-Granda et al. [32] shows that the origin in endovascular catheters increased notably.

Table 1 **Relevant publications of the incidence of candidemia (last 10 years).**

Author [reference] year of publication	Study time period	Type of study	Geographical area	Candidemia incidence per 100,000 inhabitants/year	Candidemia incidence per 1,000 admissions/year	Other Information
Pemán [15] 2012	January 2009-January 2010	Prospective	Spain		0.92	FUNGEMYCA Study
Nucci [13] 2013	November 2008-October 2010	Prospective	Latin America: Argentina, Brazil, Chile, Colombia, Ecuador, Honduras and Venezuela		1.18	Study in 21 tertiary level hospitals. 672 Episodes of candidemia 44.2% in children 36.2% in adults 19.6% in > 60 years old
Puig-Asensio [14] 2014	May 2010-April 2011	Prospective, population-based	Spain	8.1	0.98	CANDIPOP Study
Chen [24] 2014	2002-2010	Prospective	Taiwan		2.78-2.88	Study conducted at the National University Hospital
Cleveland [9] 2015	March 2008-February 2013 June 2008-May 2013	Prospective population-based	United States	In Atlanta: 14.1- 9.5 In Baltimore 30.9-14.4		3,848 cases of candidemia 85% of the patients had a central venous catheter
Hesstvedt [131] 2015	2004-2012	Prospective	Norway	3.9	0.22	Comparison the incidence obtained previously with the data obtained between 1991 and 2003
Rajendran [132] 2016	March 2012-February 2013	Prospective	United Kingdom	4.1		Blood culture isolates from 11 Scottish National Health Service boards were used
Barchiesi [133] 2016	January 2010-December 2014	Retrospective observational	Italy		1.5	
Tedeschi [134] 2016	January 2012-December 2013	Retrospective cohort, observational	Italy		2.2	
Tadec [135] 2016	January 2004-December 2010	Prospective	France		0.37	
Kocmanová [16] 2018	2012-2015	Retrospective	Czech Republic		0.21-1.22	
Mencarini [19] 2018	January 2005-December 2016	Retrospective	Italy		0.3	
Koehler [3] 2019	1990-2019	Systematic review and meta-analysis, retrospective and prospective studies	Europe	3,88	Total hospital studies without ICUs: 0.83 University hospital studies: 0.96 Studies: teaching and general hospitals 0.52	107 epidemiological studies based on the general population and epidemiological studies of hospital patients *C. albicans* was the most prevalent cause of candidasis, followed by *C. glabrata* and *C. parapsilosis*

Table 1 **Relevant publications of the incidence of candidemia (last 10 years). (cont.)**

Author [reference] year of publication	Study time period	Type of study	Geographical area	Candidemia incidence per 100,000 inhabitants/year	Candidemia incidence per 1,000 admissions/year	Other Information
Toda [136] 2019	2012-2016	Populations studies	United States	8.7		Conducted by the CDC Emerging Infections Program. 73% Of patients had a CVC
Medeiros [137] 2019	January 2011-December 2016	Retrospective cohort, observational	Brazil		2.23	
Israel [138] 2019	2005-2016	Retrospective	Israel		0.62	
Schroeder [18] 2020	2008-2017	Retrospective	Germany			Conducted in ICUs
Alobaid [11] 2021	January 2018-December 2018	Retrospective	Kuwait	5.29		Conducted at 8 major hospitals and 4 tertiary hospitals
de Oliveira [139] 2021	January 2016-December 2017	Descriptive observational	Brazil		2.7/1,000	
Nucci [12] 2021	January 2019-September 2020 January 2019-February 2020 March 2020-September 2020		Brazil		Total: 2.98 First period: 1.54 Second period: 7.44 4.76 in Non COVID-19 patients 14.80 COVID-19 Patients	
Adam [8] 2021	2004-2018	Prospective	Switzerland	2.96 - 4.20	0.09-0.1	A national survey of candidemia was conducted by the Fungal Infection Network of Switzerland (FUNGINOS). 5 university hospitals and 2 tertiary care hospitals
Suzuki [26] 2021	January 2020-December 2017	Retrospective	United States	No hospital onset:5.52	Hospital onset: 2.75/10.000 patient/day (incidence density)	A total of 130 hospitals were included. Cases are divided into hospital and non-hospital onset
Kim [25] 2021	2013-2018	Retrospective	Republic of Korea		0.43-1.33	Tertiary care hospital
Mareković [35] 2021	2018-2020	Retrospective observational	Croatia		0.47-0.69	The main risk factor is CVC. C. parapsilosis is associated with CVC in ICUs
Mamali [10] 2022	2009-2018	Retrospective	Greece	8.56		
Chibabhai [17] 2022	January 2016-December 2020	Retrospective	South Africa		2.9	
Mirza [140] 2022	2009-2010	Prospective observational	Turkey		0.94	

CDC: Centers for Disease Control and Prevention; CVC, central venous catheter; ICU, intensive care unit.

Table 2 Incidence and relationship of candidemia with COVID-19.

Author [reference] year of publication	Study time period	Type of study	Geographical area	Candidemia in patients with COVID-19 per 1,000 admissions-year	Candidemia in patients without COVID-19 per 1,000 admissions-year	Candidemia in ICU		Mortality in patients with candidemia		Other Information
						With COVID-19	Without COVID-19	With COVID-19	Without COVID-19	
Kayaaslan [141] 2021	March 2019-March 2021	Retrospective	Turkey			2.16/1,000 admissions/year	1.06 /1,000 admissions/year	87.5 (28-day Mortality) Death: 92.5%	67.9 (28-day Mortality) Death: 79.4%	Study in ICU, tertiary hospital. Division of study years between pre-pandemic and pandemic
Nucci [12] 2021	Period 1: January 2019-February 2020	Retrospective	Brazil	1.54		77.8%	50% 31.2%	66.7% (30-day Mortality)	56.3% (30-day Mortality)	In public tertiary care hospital
	Period 2: March 2020- September 2020			7.44	4.76				62.5% (30-day Mortality)	
Mastrangelo [30] 2021	February 2020-June 2020	Prospective and retrospective cohort	Italy	1.1	0.15	66.7%	29.4%	57.1%	58.8%	They compared the data to a 2017 historical cohort
Macauley [142] 2021	May 2014-October 2020	Retrospective	United States			51/1,000 admissions/year	11/1,000 admissions/year	75%	61%	Medical ICU candidemia episodes occurring in non-oncology hospitals were analyzed
Rajni [143] 2021	August 2020-January 2021	Retrospective	India			14-15/1,000 admissions/year	5-7/1,000 admissions/year			The study is performed in 2 ICUs
Machado [31] 2022	January 2019-December 2020	Retrospective	Spain	4.73	0.85	71.9%	32.4%	62.5%	46.5%	
Ayalon [144] 2022	September 2020-March 2020	Retrospective case-control study	Israel			1.7/1,000 admissions/year	3.5/1,000 admissions/year	90.9%		Performed in a tertiary hospital in critically ill patients with COVID-19

ICU, intensive care unit.

Conclusion:

Data on the incidence of candidemia in recent years are irregular and imprecise, both with population denominators and by number of hospital admissions. In addition, trends are highly variable with upward and downward trends in recent years in different countries.

The limited data on this aspect during the COVID-19 pandemic, point to a clear increase in the incidence of candidemia in COVID-19 patients and during the COVID-19 period.

WHAT PROPORTION OF CANDIDEMIC EPISODES ARE RELATED TO ENDOVASCULAR CATHETERS?

The majority of patients who develop candidemia described in the literature have a central venous catheter (CVC) in place [33-36] with an estimated value between 73% [37] and 94% [38, 39] although not always the catheter is the origin of the episode.

Table 3 lists the articles showing the figures of catheter-related candidemias since approximately 2010, defined according to the Infectious Diseases Society of America (IDSA) guidelines [40]. It ranges from 29% [41] to 52% [1], with a median of 36.6%.

It should be noted that, most of the studies have a retrospective character and, in addition, in some of them it is not clarified whether the origin in the catheter is proven or is presumptive. Another of the biases in some of the articles is based on the type of patients selected. In the case of intensive care patients, practically all of them have a central catheter and in the vast majority of the candidemias are so considered primary. The catheter was therefore indirectly assumed to be the cause but not proved [14,33,38].

Conclusion:

The biases of the existing studies do not allow us to accurately determine the real proportion of candidemias that have an unquestionable origin in a vascular catheter. The data suggest that 30-50% would be acceptable estimates at this time.

Table 3 Main articles reporting the proportion of catheter-related candidemia.

Author [reference] year of publication	Study time period	Type of study	Geographical area	Proportion of catheter related candidemia (CRC)	Diagnosis Method	Other Information
Garnacho-Montero [38] 2013	January 2004 June 2009	Prospective	Spain	43.6%	Estimated	Study of patients with CVC
Puig-Asensio [14] 2014	May 2010 April 2011	Prospective population-based	Spain	34.3%	Microbiological proof	CANDIPOP Study
Tadec [135] 2016	January 2004-December 2010	Retrospective	France	38.1%	Estimated	
Arias [4] 2017	January 2006-December 2013	Retrospective cohorts	Brussels	37%	Microbiological proof	Single-center. Hospitalized>48h. CVC>48h
Jia [145] 2018	January 2011 December 2016	Retrospective	China	34.4%	Microbiological proof	
Brunetti [20] 2019	January 2011 December 2016	Retrospective	Italy	32.03%	Microbiological proof	There was an increase in *Candida* spp. BSIs
Lee [5] 2019	January 2010-December 2017	Retrospective	South Korea	41.8%	Microbiological proof	
Ohki [33] 2020	January 2007-December 2016	Retrospective observational	Japan	44%	Microbiological proof	The study was carried out in ICU patients. 79.6% of the patients had a CVC
Gits-Muselli [34] 2020	October 2010-September 2017	Retrospective	France	30.5%	Microbiological proof	Most of them were oncology patients (85.7%)
Liu [146] 2021	January 2013- June 2020	Retrospective observational	China	33.2%	Microbiological proof	
Asai [1] 2021	September 2014-May 2018	Retrospective	Japan	52%	Not specified	Evaluated the performance of SOFA to determine these verity and prognosis of candidemia
Moreno-García [39] 2021	2007-2016	Retrospective	Spain	36.2%	Microbiological proof	
Papadimitriou-Olivgeris [41] 2022	2014-2021	Retrospective	Switzerland	29%	Microbiological proof	They wanted to identify predictors of mortality in patients with candidemia. Most candidemias were of unknown origin
Aydin [88] 2022	January 2013-December 2019	Retrospective	Turkey	37.7%	Microbiological proof	

CRC, catheter related candidemia; CVC, central venous catheter; ICU, intensive care unit.

WHAT IS THE BEST WAY TO PROCESS A WITHDRAWAL CATHETER TO ESTABLISH *CANDIDA* SPP. COLONIZATION?

The gold standard for the detection of candidemia in the catheter tip is the semi-quantitative catheter rolling surface method described by Maki et al [42]. It is a quick and simple technique widely used in microbiology laboratories.

Subsequently, different techniques have been proposed to try to improve on the Maki's technique, such as the quantitative method of Cleri et al. based on flushing of the catheter lumen with culture medium [43]; or the subsequent modification carried out by Liñares et al. [44]. Brun-Buisson et al. developed a technique based on vortex shaking of a segment of the catheter [45]. Sonication of the catheter, previously introduced in an enrichment medium, was then performed. A higher sensitivity was obtained than with the semi-quantitative method [46].

Some results however, reported by other researchers, show that the sonication method had no advantage over Maki's technique in CVC cultures. In addition, the two techniques together are less efficient [47]. In contrast, some authors propose sonication of the previously fragmented catheter tip. They conclude that this method can be complementary to the Maki's technique [48]. Unfortunately, none of these techniques were studied specifically for *Candida* spp. and none of the article describes the superiority of one process over another.

Bouza et al. were able to demonstrate in a randomized study of 1,000 catheters that quantitative sonication techniques and vortexing techniques were not superior to the Maki's procedure [49].

Therefore, setting a strict value of a certain number of *Candida* spp. colony forming units (cfu) to establish as significant the colonization of a catheter segment has not been adequate assessed. We now recommend that any *Candida* spp. growth obtained by a semi-quantitative or quantitative method in endovascular catheter segments are suggestive of being the origin of a candidemia if there are no obvious alternative origins.

Concerning the complementary value of PCR techniques performed at the catheter tip, the data are inconclusive at present [50-52].

Conclusion:

The presence of *Candida* spp. of the same species of the blood isolates on the tip or another endovascular fragment of the catheter in any count, establishes, in our opinion, the origin of the candidemia, unless there are obvious alternative sources. No single culture method has demonstrated superiority over another, but performing more than one may be complementary.

CAN A DIAGNOSIS OF CATHETER-RELATED CANDIDEMIA BE ESTABLISHED WITHOUT REMOVING AND CULTURING CATHETER ENDOVASCULAR SEGMENTS?

The methods used to establish the origin of catheter-related bacteremia without removing the catheter have been several and only relatively successful [49]. Differential quantitative blood cultures comparing the number of colonies per milliliter of blood between samples obtained through any catheter lumen and those obtained through peripheral veins are classic in patients with bacterial infection [53]. It is accepted that 3-fold greater than the colony count from blood obtained from the catheter and peripheral line have a high positive predictive value (PPV) and negative predictive value (NPV) for establishing the catheter as the source of bacteremia [40,54-56].

However, it is a common mistake to automatically extrapolate results in patients with bacteremia to the case of catheter-related candidemia (CRC) [6,57,58].

Classical blood colony counting methods were replaced by lysis-centrifugation blood cultures. Bille et al. proposed that this technique could be useful for the detection of fungemia after catheter removal or in patients treated with antifungals [59]. Nevertheless, lysis-centrifugation is a practice that is not commonly used today due to its technical difficulties. It is associated with frequent contamination and dangerous handling [60-62].The alternative has been the differential time to positivity (DTP) between blood obtained through catheter lumens and peripheral veins in classic blood cultures (BC). Again, the differentials valid in bacteremia do not necessarily apply to fungemia.

Several articles studying time differentials as a distinguishing feature of catheter-related candidemia do not, from our point of view, use adequate controls. In addition, the estimation of valid differential times is highly variable between papers and with different *Candida* species [34,63-66].

Fernandez-Cruz et al. prospectively evaluated different methods to establish CRC such as: superficial skin Gram stain and culture, Kite technique, BC, DTP and time to positivity (TTP). None of the non-invasive techniques studied individually were sufficient to rule out the catheter as the source of candidemia before removal [6,57].

Ben-Ami et al. proposed that a TTP<30 hours may suggest that the candidemia have an origin in the catheter [67], but this absolute value has not been proven valid in other studies [6,57,63].

Finally, neither the study of superficial (peri-catheter skin) *Candida* spp. colonization nor molecular techniques on the catheter have provided clear criteria for clinical use [52,68].

Conclusion:

In our opinion, there is no conservative confirmatory catheter procedure that can affirm or reject that the catheter is the source of the candidemia. It should not be assumed that the results obtained for bacteremic infections can be applied to candidemia.

WHAT IS THE VALUE OF DETECTING *CANDIDA* SPP. EXCLUSIVELY FROM THE ENDOVASCULAR CATHETER IN PATIENTS WITH SIMULTANEOUS NEGATIVE BLOOD CULTURES?

A high proportion (73.4-81%) of the patients with *Candida* spp. isolated in catheter tips do not have concurrent candidemia results [69,70]. At present, the meaning of a positive culture of *Candida* spp. in an endovascular catheter segment of the removed catheter tip or by extraction of blood obtained through the catheter lumens, in patients with simultaneous negative peripheral BC, is under discussion.

Studies assessing this issue are retrospective and with a limited number of patients but all agree that this should not automatically imply the administration of antifungal agents. Mortality rates of treated and untreated cases were similar one year after [57,71-74].

The risk of a subsequent development of candidemia appears to be low in these circumstances and it ranges from 4% to 12% [69,75].

Conclusion:

Isolation of *Candida* spp. from the catheter or from blood taken through the catheter in patients with concurrent negative peripheral BC for *Candida* spp. does not routinely indicate antifungal therapy.

IS *CANDIDA* SPP. COLONIZATION OF THE SKIN OR CATHETER HUBS (SUPERFICIAL CULTURES) A GOOD PREDICTOR OF COLONIZATION OF ENDOVASCULAR SEGMENTS OF THE CATHETER?

We define as superficial cultures a set of cultures from the skin surrounding the catheter entry point (3 cm) and all catheter hubs [52,76,77].

Superficial cultures have high NPVs (98%) but relatively low PPVs (34-61%) and have not been specifically designed for *Candida* spp. infections. Therefore, in our opinion, they constitute, despite the existing literature, a method under study that cannot be used as a clinical test for episodes of candidemia [68,76,78-82].

Conclusion:

The data currently available do not allow using the presence of *Candida* spp. colonization of the catheter hubs or skin surrounding the catheter entrance to estimate yeast colonization in the endovascular catheter segments.

ARE THERE *CANDIDA* SPECIES THAT PARTICULARLY POINT TO AN ORIGIN IN THE CATHETER?

Any *Candida* species can cause CRC, and the proportions are variable from one species to another as can be seen in the data collected in Table 4. Currently, there is no close relationship between any particular species of *Candida* and catheter colonization.

However, some authors have suggested that the isolation of *Candida parapsilosis* in blood would indicate an endovascular origin [20,35,83,84]. It should be noted that this has not been confirmed in other studies and most of the literature does not specify the type of species concretely isolated in the CVC [4,14,33,34,37,39,41,57,85-88].

Conclusion:

Although *C. parapsilosis* has been associated with CRC, current information does not allow to establish a relationship between any specific *Candida* species and the catheter.

WHAT IS THE DIAGNOSTIC AND PROGNOSTIC VALUE OF *CANDIDA* SPP. BIOMARKERS IN THE DETECTION OF CANDIDEMIA OF ANY ORIGIN?

The most common biomarkers employed for the detection of *Candida* spp. are: mannan and anti-mannan, *Candida* germ tube antibodies (CAGTA), 1-3-β-D-glucan (BDG) and the detection of fungal DNA in blood [51,89-93].

Mannan antigen is a constituent of the cell wall of *Candida* spp. detectable in serum from colonized patients. It has a low sensitivity due to its rapid elimination from the bloodstream. Despite this, the diagnosis of candidemia can be improved by increasing the specificity by combining techniques such as, for example, with the detection of human anti-mannan antibodies in serum or plasma [7,94,95]. Meng et al. obtained better results with *Candida* IgM anti-mannan antibodies than with IgG antibodies; although a higher sensitivity (93%) was achieved with the combination of both. Mannan-antimannan can provide an early diagnosis of candidemia [96,97].

Specific *Candida* germ tube antibody detection (CAGTA) [7,8] has a sensitivity of around 66% and a specificity of 76% for candidemia [90]. It can be used for the diagnosis of invasive candidiasis [99] and it could be used as a prognostic marker because a higher amount of antibodies is related to a better evolution in severe patients [90]. Martínez-Jimenez et al. achieved 100% sensitivity combining CAGTA and BDG with CAGTA and mannan antigens to detect candidemia by three *Candida* species. The NPV was approximately 97% in both cases [100].

The BDG is a non-specific *Candida* spp. test that is released with infection and is detectable in serum and blood. Its sensitivity in patients with candidemia ranges from 75-80% and its specificity is approximately 80% [91,101]. Its main limitations are positivity in non-*Candida* spp. fungal infections and the existence of false positives in several situations [102,103].

Candida spp. DNA detection in blood is a promising technique [91] but its main limitations include lack of sensitivity, reproducibility and accuracy for clinical use [7,104-107].

Table 4 Some examples of articles that show *Candida* species isolated from the catheter.

Author [reference] year of publication	Type of article and study period	Objective	Distribution of *Candida* species in CRC episodes
Bouza [57] 2013	Retrospective July 2005- August 2010	Assess efficacy of TTP, DTP, peripheral BC and CVC and number of positive BC as CRC markers	*C. albicans* 48.2% *C. parapsilosis* 33.9% *C. glabrata* 10.7% *C. tropicalis* 5.4% C. *guilliermondii* 1.8%
Arias [4] 2017	Retrospective cohort January 2006 - December 2013	Comparison of mortality, epidemiology and morbidity in patients with candidemia, with and without relation to CVC	*Candida albicans* 62% *Candida* non-*albicans* 38% *C. parapsilosis* 16.67% *C. glabrata* 12.5% *C. tropicalis* 8.34%
Brunetti [20] 2019	Retrospective January 2011- December 2016	Evaluation of the cumulative annual incidence of candidemia episodes, analyzing the type of species, presence of intravascular devices and distribution among the different wards of the hospital and biofilm study	*C. parapsilosis* 51.53% *C. albicans* 34.18% *C. glabrata* 6.12% *C. tropicalis* 6.12% Other 2.5%
Gits-Muselli [34] 2020	Retrospective October 2010-September 2017	Evaluation of TTP and DTP to assess catheter-related yeast fungemia	*C. albicans* 41% *C. glabrata* 22% *C. parapsilosis* 16% *C. tropicalis* 9% *C. lusitaniae* 3% Other 9%

Abbreviations: BC, blood culture; CRC, catheter related candidemia; CVC, central venous catheter; DTP, differential time to positivity; TTP, time to positivity.

The use of any of these biomarkers, alone or in combination, during the treatment of confirmed candidemia is of significant interest. It could convert treatments of standard duration into treatments of shorter duration according to the patient's needs or provide early information on therapeutic failures. Data in this regard in the literature are very limited [7,94,97,100,108-114].

Conclusion:

Candida spp. biomarkers can be used for the diagnosis of candidemia providing better results when used together. Their prognostic value and their use as markers of end of treatment are far from being achieved.

MAY *CANDIDA* SPP. BIOMARKERS HELP TO ESTABLISH THE DIAGNOSIS OF CATHETER-RELATED CANDIDEMIA?

Candida spp. biomarkers have not been used specifically to determine the point of origin in patients with candidemia. Some studies suggest that candidemias from catheter origin would be more frequently associated with negativity of these tests [115-117].

In a study conducted by Agnelli et al. in Madrid, they proved that successive negative BDG results in patients with proven candidemia were associated with higher CRC cases and a milder level of disease [117]. Other authors, also suggest this idea [116]. Dobiáš et al. obtained lower BDG concentrations in patients with CRC compared to patients with probable deep-seated candidemia [118]. However, it should be noted that no BDG cut-off values for candidemia have been firmly established.

Preliminary data wanted to determine if CAGTA detection in patients with candidemia was related to the origin of the infection. Additionally, they concluded that negative results for CAGTA, in patients with candidemia, could likely indicate that the disease lacks deep invasion and has a catheter origin [115,119].

We have not found quantitative comparisons of biomarkers as a tool to differentiate candidemia with origin in the catheter or with other origins.

Conclusion:

The literature available does not allow to determine if _Candida_ spp. biomarkers detection could be used to establish the origin of candidemias in the catheter. We consider this as an unresolved issue and in need of research.

WHAT IS THE PERFORMANCE OF T2 MAGNETIC

RESONANCE (T2MR) CANDIDEMIA DETECTION? ARE THERE STUDIES IN THE FIELD OF CATHETER-RELATED CANDIDEMIA?

Candida T2 Magnetic Resonance (T2MR) is a non-culture based, fully automated nanotechnology PCR multiplex used for the diagnosis of candidemia from whole blood without previous isolation. It is able to identify the most common *Candida* species (*Candida albicans*, *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei* and *Candida glabrata*) in approximately 3-5 hours. In addition, the detection limit is very low, 1-3 cfu/ml whole blood [120]. This method has a high sensitivity (91.1-100%) and specificity (97.8%-98.9%) for those species [121-124].

The use of T2MR may influence the reduction of empirical antifungal treatment time and thus establish drug administration times [125]. In one prospective and multicenter study, conducted by Muñoz et al., the T2MR assay allowed early detection and better prediction of the risk of complicated candidemia than the one obtained with conventional BCs or BDG [126]. In another study, it was estimated that a persistently positive T2MR value in candidemic patients could be associated with a higher risk of poor prognosis, with a specificity and PPV of 100% and NPV of 79.6%. Furthermore, the combination of this technique with standard cultures showed a better discriminative ability to recognize patients with risk of death or development of invasive candidiasis, compared to the combination of T2MR with biomarkers [127].

Consistent with the above, in 2021 Steuber et al. stipulated a reduction in detection time from 41 hours with BC to 9 with T2MR. In addition, the time to antifungal administration was considerably shorter in the T2MR group than in the BC group (4 hours vs. 37) [122]. Other authors report similar results [123,128-130].

The main limitations of this technique are its methodological applicability, which does not make it applicable to all suspected BCs and its high price [125]. We have not found literature that specifically applies T2MR techniques to the search for the origin of candidemic episodes.

Conclusion:

Candidemia detection with T2 technique has, in addition to a diagnostic interest, a potential applicability to the knowledge of the pathogenesis and duration of treatment in candidemic patients. They have not been used as tools to determine the origin of candidemia.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Asai N, Ohashi W, Sakanashi D, Suematsu H, Kato H, Hagihara M, et al. Combination of Sequential Organ Failure Assessment (SOFA) score and Charlson Comorbidity Index (CCI) could predict the severity and prognosis of candidemia more accurately than the Acute Physiology, Age, Chronic Health Evaluation II (APACHE II) score. BMC Infect Dis. 2021;21(1):77. DOI: 10.1186/s12879-020-05719-8
2. Morgan J, Meltzer MI, Plikaytis BD, Sofair AN, Huie-White S, Wilcox S, et al. Excess mortality, hospital stay, and cost due to candidemia: a case-control study using data from population-based candidemia surveillance. Infect Control Hosp Epidemiol. 2005;26(6):540-7. DOI: 10.1086/502581
3. Koehler P, Stecher M, Cornely OA, Koehler D, Vehreschild M, Bohlius J, et al. Morbidity and mortality of candidaemia in Europe: an epidemiologic meta-analysis. Clin Microbiol Infect. 2019;25(10):1200-12. DOI: 10.1016/j.cmi.2019.04.024
4. Arias S, Denis O, Montesinos I, Cherifi S, Miendje Deyi VY, Zech F. Epidemiology and mortality of candidemia both related and unrelated to the central venous catheter: a retrospective cohort study. Eur J Clin Microbiol Infect Dis. 2017;36(3):501-7. DOI: 10.1007/s10096-016-2825-3
5. Lee YM, Kim DY, Kim YJ, Park KH, Lee MS. Clinical impacts of delayed central venous catheter removal according to the severity of comorbidities in patients with candidaemia. J Hosp Infect. 2019;103(4):420-7. DOI: 10.1016/j.jhin.2019.08.018
6. Fernández-Cruz A, Martín-Rabadán P, Suárez-Salas M, Rojas-Wettig L, Pérez MJ, Guinea J, et al. Is it feasible to diagnose catheter-related candidemia without catheter withdrawal? Med Mycol. 2014;52(5):491-7. DOI: 10.1093/mmy/myu013
7. Pitarch A, Nombela C, Gil C. Diagnosis of Invasive Candidiasis: From Gold Standard Methods to Promising Leading-edge Technologies. Curr Top Med Chem. 2018;18(16):1375-92. DOI: 10.2174/1568026618666181025093146
8. Adam KM, Osthoff M, Lamoth F, Conen A, Erard V, Boggian K, et al. Trends of the Epidemiology of Candidemia in Switzerland: A 15-Year FUNGINOS Survey. Open Forum Infect Dis. 2021;8(10):ofab471.

DOI: 10.1093/ofid/ofab471

9. Cleveland AA, Harrison LH, Farley MM, Hollick R, Stein B, Chiller TM, et al. Declining incidence of candidemia and the shifting epidemiology of Candida resistance in two US metropolitan areas, 2008-2013: results from population-based surveillance. PLoS One. 2015;10(3):e0120452. DOI: 10.1371/journal.pone.0120452
10. Mamali V, Siopi M, Charpantidis S, Samonis G, Tsakris A, Vrioni G, et al. Increasing Incidence and Shifting Epidemiology of Candidemia in Greece: Results from the First Nationwide 10-Year Survey. J Fungi (Basel). 2022;8(2). DOI: 10.3390/jof8020116
11. Alobaid K, Ahmad S, Asadzadeh M, Mokaddas E, Al-Sweih N, Albenwan K, et al. Epidemiology of Candidemia in Kuwait: A Nationwide, Population-Based Study. J Fungi (Basel). 2021;7(8). DOI: 10.3390/jof7080673
12. Nucci M, Barreiros G, Guimarães LF, Deriquehem VAS, Castiñeiras AC, Nouér SA. Increased incidence of candidemia in a tertiary care hospital with the COVID-19 pandemic. Mycoses. 2021;64(2):152-6. DOI: 10.1111/myc.13225
13. Nucci M, Queiroz-Telles F, Alvarado-Matute T, Tiraboschi IN, Cortes J, Zurita J, et al. Epidemiology of candidemia in Latin America: a laboratory-based survey. PLoS One. 2013;8(3):e59373. DOI: 10.1371/journal.pone.0059373
14. Puig-Asensio M, Padilla B, Garnacho-Montero J, Zaragoza O, Aguado JM, Zaragoza R, et al. Epidemiology and predictive factors for early and late mortality in Candida bloodstream infections: a population-based surveillance in Spain. Clin Microbiol Infect. 2014;20(4):O245-54. DOI: 10.1111/1469-0691.12380
15. Pemán J, Cantón E, Quindós G, Eraso E, Alcoba J, Guinea J, et al. Epidemiology, species distribution and in vitro antifungal susceptibility of fungaemia in a Spanish multicentre prospective survey. J Antimicrob Chemother. 2012;67(5):1181-7. DOI: 10.1093/jac/dks019
16. Kocmanová I, Lysková P, Chrenkova V, Olišarová P, Dobiáš R, Janouškovcová H, et al. Nosocomial candidemia in the Czech Republic in 2012-2015: results of a microbiological multicentre study. Epidemiol Mikrobiol Imunol. 2018;67(1):3-10.
17. Chibabhai V. Incidence of candidemia and prevalence of azole-resistant candidemia at a tertiary South African hospital - A retrospective laboratory analysis 2016-2020. S Afr J Infect Dis. 2022;37(1):326. DOI: 10.4102/sajid.v37i1.326
18. Schroeder M, Weber T, Denker T, Winterland S, Wichmann D, Rohde H, et al. Epidemiology, clinical characteristics, and outcome of candidemia in critically ill patients in Germany: a single-center retrospective 10-year analysis. Ann Intensive Care. 2020;10(1):142. DOI: 10.1186/s13613-020-00755-8
19. Mencarini J, Mantengoli E, Tofani L, Riccobono E, Fornaini R, Bartalesi F, et al. Evaluation of candidemia and antifungal consumption in a large tertiary care Italian hospital over a 12-year period. Infection. 2018;46(4):469-76. DOI: 10.1007/s15010-018-1139-z
20. Brunetti G, Navazio AS, Giuliani A, Giordano A, Proli EM, Antonelli G, et al. Candida blood stream infections observed between 2011 and 2016 in a large Italian University Hospital: A time-based retrospective analysis on epidemiology, biofilm production, antifungal agents consumption and drug-susceptibility. PLoS One. 2019;14(11):e0224678. DOI: 10.1371/journal.pone.0224678
21. Siopi M, Tarpatzi A, Kalogeropoulou E, Damianidou S, Vasilakopoulou A, Vourli S, et al. Epidemiological Trends of Fungemia in Greece with a Focus on Candidemia during the Recent Financial Crisis: a 10-Year Survey in a Tertiary Care Academic Hospital and Review of Literature. Antimicrob Agents Chemother. 2020;64(3). DOI: 10.1128/aac.01516-19
22. Spiers R, Smyth B, Lamagni T, Rooney P, Dorgan E, Wyatt T, et al. The epidemiology and management of candidemia in Northern Ireland during 2002-2011, including a 12-month enhanced case review. Med Mycol. 2019;57(1):23-9. DOI: 10.1093/mmy/myx165
23. Ulu Kilic A, Alp E, Cevahir F, Ture Z, Yozgat N. Epidemiology and cost implications of candidemia, a 6-year analysis from a developing country. Mycoses. 2017;60(3):198-203. DOI: 10.1111/myc.12582
24. Chen PY, Chuang YC, Wang JT, Sheng WH, Yu CJ, Chu CC, et al. Comparison of epidemiology and treatment outcome of patients with candidemia at a teaching hospital in Northern Taiwan, in 2002 and 2010. J Microbiol Immunol Infect. 2014;47(2):95-103. DOI: 10.1016/j.jmii.2012.08.025
25. Kim JH, Suh JW, Kim MJ. Epidemiological Trends of Candidemia and the Impact of Adherence to the Candidemia Guideline: Six-Year Single-Center Experience. J Fungi (Basel). 2021;7(4). DOI: 10.3390/jof7040275
26. Suzuki H, Perencevich EN, Diekema DJ, Livorsi DJ, Nair R, Kralovic SM, et al. Temporal Trends of Candidemia Incidence Rates and Potential Contributions of Infection Control Initiatives Over 18 Years Within the United States Veterans Health Administration System: A Joinpoint Time-Series Analysis. Clin Infect Dis. 2021;73(4):689-96. DOI: 10.1093/cid/ciab105
27. Kajihara T, Yahara K, Nagi M, Kitamura N, Hirabayashi A, Hosaka Y, et al. Distribution, trends, and antifungal susceptibility of Candida species causing candidemia in Japan, 2010-2019: A retrospective observational study based on national surveillance data. Med Mycol. 2022. DOI: 10.1093/mmy/myac071
28. Braga PR, Cruz IL, Ortiz I, Barreiros G, Nouér SA, Nucci M. Secular trends of candidemia at a Brazilian tertiary care teaching hospital. Braz J Infect Dis. 2018;22(4):273-7. DOI: 10.1016/j.bjid.2018.07.008
29. Ricotta EE, Lai YL, Babiker A, Strich JR, Kadri SS, Lionakis MS, et al. Invasive Candidiasis Species Distribution and Trends, United States, 2009-2017. J Infect Dis. 2021;223(7):1295-302. DOI: 10.1093/infdis/jiaa502
30. Mastrangelo A, Germinario BN, Ferrante M, Frangi C, Li Voti R, Muccini C, et al. Candidemia in Coronavirus Disease 2019 (COVID-19) Patients: Incidence and Characteristics in a Prospective Cohort Compared With Historical Non-COVID-19 Controls. Clin Infect Dis. 2021;73(9):e2838-e9. DOI: 10.1093/cid/ciaa1594
31. Machado M, Estévez A, Sánchez-Carrillo C, Guinea J, Escribano P, Alonso R, et al. Incidence of Candidemia Is Higher in COVID-19 versus Non-COVID-19 Patients, but Not Driven by Intrahospital Transmission. J Fungi (Basel). 2022;8(3). DOI: 10.3390/jof8030305
32. Pérez-Granda MJ, Carrillo CS, Rabadán PM, Valerio M, Olmedo M, Muñoz P, et al. Increase in the frequency of catheter-relat-

ed bloodstream infections during the COVID-19 pandemic: a plea for control. J Hosp Infect. 2022;119:149-54. DOI: 10.1016/j.jhin.2021.09.020

33. Ohki S, Shime N, Kosaka T, Fujita N. Impact of host- and early treatment-related factors on mortality in ICU patients with candidemia: a bicentric retrospective observational study. J Intensive Care. 2020;8:30. DOI: 10.1186/s40560-020-00450-7
34. Gits-Muselli M, Villiers S, Hamane S, Berçot B, Donay JL, Denis B, et al. Time to and differential time to blood culture positivity for assessing catheter-related yeast fungaemia: A longitudinal, 7-year study in a single university hospital. Mycoses. 2020;63(1):95-103. DOI: 10.1111/myc.13024
35. Mareković I, Pleško S, Rezo Vranješ V, Herljević Z, Kuliš T, Jandrlić M. Epidemiology of Candidemia: Three-Year Results from a Croatian Tertiary Care Hospital. J Fungi (Basel). 2021;7(4). DOI: 10.3390/jof7040267
36. Poissy J, Damonti L, Bignon A, Khanna N, Von Kietzell M, Boggian K, et al. Risk factors for candidemia: a prospective matched case-control study. Crit Care. 2020;24(1):109. DOI: 10.1186/s13054-020-2766-1
37. Nucci M, Braga PR, Nouér SA, Anaissie E. Time of catheter removal in candidemia and mortality. Braz J Infect Dis. 2018;22(6):455-61. DOI: 10.1016/j.bjid.2018.10.278
38. Garnacho-Montero J, Díaz-Martín A, García-Cabrera E, Ruiz Pérez de Pipaón M, Hernández-Caballero C, Lepe-Jiménez JA. Impact on hospital mortality of catheter removal and adequate antifungal therapy in Candida spp. bloodstream infections. J Antimicrob Chemother. 2013;68(1):206-13. DOI: 10.1093/jac/dks347
39. Moreno-García E, Puerta-Alcalde P, Gariup G, Fernández-Ruiz M, López Cortés LE, Cuervo G, et al. Early Stepdown From Echinocandin to Fluconazole Treatment in Candidemia: A Post Hoc Analysis of Three Cohort Studies. Open Forum Infect Dis. 2021;8(6):ofab250. DOI: 10.1093/ofid/ofab250
40. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49(1):1-45. DOI: 10.1086/599376
41. Papadimitriou-Olivgeris M, Battistolo J, Poissy J, Coste A, Bochud PY, Calandra T, et al. Key Role of Early Source Control in Candidemic Patients With Sepsis or Septic Shock. Open Forum Infect Dis. 2022;9(8):ofac383. DOI: 10.1093/ofid/ofac383
42. Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous-catheter-related infection. N Engl J Med. 1977;296(23):1305-9. DOI: 10.1056/nejm197706092962301
43. Cleri DJ, Corrado ML, Seligman SJ. Quantitative culture of intravenous catheters and other intravascular inserts. J Infect Dis. 1980;141(6):781-6. DOI: 10.1093/infdis/141.6.781
44. Liñares J, Sitges-Serra A, Garau J, Pérez JL, Martín R. Pathogenesis of catheter sepsis: a prospective study with quantitative and semiquantitative cultures of catheter hub and segments. J Clin Microbiol. 1985;21(3):357-60. DOI: 10.1128/jcm.21.3.357-360.1985
45. Brun-Buisson C, Abrouk F, Legrand P, Huet Y, Larabi S, Rapin M. Diagnosis of central venous catheter-related sepsis. Critical level of quantitative tip cultures. Arch Intern Med. 1987;147(5):873-7.
46. Sherertz RJ, Raad, II, Belani A, Koo LC, Rand KH, Pickett DL, et al. Three-year experience with sonicated vascular catheter cultures in a clinical microbiology laboratory. J Clin Microbiol. 1990;28(1):76-82. DOI: 10.1128/jcm.28.1.76-82.1990
47. Slobbe L, El Barzouhi A, Boersma E, Rijnders BJ. Comparison of the roll plate method to the sonication method to diagnose catheter colonization and bacteremia in patients with long-term tunnelled catheters: a randomized prospective study. J Clin Microbiol. 2009;47(4):885-8. DOI: 10.1128/jcm.00998-08
48. Guembe M, Martín-Rabadán P, Cruces R, Pérez Granda MJ, Bouza E. Sonicating multi-lumen sliced catheter tips after the roll-plate technique improves the detection of catheter colonization in adults. J Microbiol Methods. 2016;122:20-2. DOI: 10.1016/j.mimet.2016.01.004
49. Bouza E, Alvarado N, Alcalá L, Sánchez-Conde M, Pérez MJ, Muñoz P, et al. A prospective, randomized, and comparative study of 3 different methods for the diagnosis of intravascular catheter colonization. Clin Infect Dis. 2005;40(8):1096-100. DOI: 10.1086/428576
50. Marcos-Zambrano LJ, Escribano P, Bouza E, Guinea J. [Use of molecular typing tools for the study of hospital outbreaks of candidemia]. Rev Iberoam Micol. 2014;31(2):97-103. DOI: 10.1016/j.riam.2013.06.003
51. Koc Ö, Kessler HH, Hoenigl M, Wagener J, Suerbaum S, Schubert S, et al. Performance of Multiplex PCR and β-1,3-D-Glucan Testing for the Diagnosis of Candidemia. J Fungi (Basel). 2022;8(9). DOI: 10.3390/jof8090972
52. Chaves F, Garnacho-Montero J, Del Pozo JL, Bouza E, Capdevila JA, de Cueto M, et al. Diagnosis and treatment of catheter-related bloodstream infection: Clinical guidelines of the Spanish Society of Infectious Diseases and Clinical Microbiology and (SEIMC) and the Spanish Society of Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC). Med Intensiva (Engl Ed). 2018;42(1):5-36. DOI: 10.1016/j.medin.2017.09.012
53. Mosca R, Curtas S, Forbes B, Meguid MM. The benefits of Isolator cultures in the management of suspected catheter sepsis. Surgery. 1987;102(4):718-23.
54. Telenti A, Steckelberg JM, Stockman L, Edson RS, Roberts GD. Quantitative blood cultures in candidemia. Mayo Clin Proc. 1991;66(11):1120-3. DOI: 10.1016/s0025-6196(12)65791-7
55. Quilici N, Audibert G, Conroy MC, Bollaert PE, Guillemin F, Welfringer P, et al. Differential quantitative blood cultures in the diagnosis of catheter-related sepsis in intensive care units. Clin Infect Dis. 1997;25(5):1066-70. DOI: 10.1086/516090
56. Capdevila JA, Planes AM, Palomar M, Gasser I, Almirante B, Pahissa A, et al. Value of differential quantitative blood cultures in the diagnosis of catheter-related sepsis. Eur J Clin Microbiol Infect Dis. 1992;11(5):403-7. DOI: 10.1007/bf01961854
57. Bouza E, Alcalá L, Muñoz P, Martín-Rabadán P, Guembe M, Rodríguez-Créixems M. Can microbiologists help to assess catheter involvement in candidaemic patients before removal? Clin Microbiol Infect. 2013;19(2):E129-35. DOI: 10.1111/1469-0691.12096

58. Yagupsky P, Nolte FS. Quantitative aspects of septicemia. Clin Microbiol Rev. 1990;3(3):269-79. DOI: 10.1128/cmr.3.3.269

59. Bille J, Edson RS, Roberts GD. Clinical evaluation of the lysis-centrifugation blood culture system for the detection of fungemia and comparison with a conventional biphasic broth blood culture system. J Clin Microbiol. 1984;19(2):126-8. DOI: 10.1128/jcm.19.2.126-128.1984

60. Idelevich EA, Grünastel B, Becker K. Rapid Detection and Identification of Candidemia by Direct Blood Culturing on Solid Medium by Use of Lysis-Centrifugation Method Combined with Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOF MS). J Clin Microbiol. 2017;55(1):97-100. DOI: 10.1128/jcm.01787-16

61. Ombelet S, Natale A, Ronat JB, Kesteman T, Vandenberg O, Jacobs J, et al. Biphasic versus monophasic manual blood culture bottles for low-resource settings: an in-vitro study. Lancet Microbe. 2022;3(2):e124-e32. DOI: 10.1016/s2666-5247(21)00241-x

62. Kiehn TE, Wong B, Edwards FF, Armstrong D. Comparative recovery of bacteria and yeasts from lysis-centrifugation and a conventional blood culture system. J Clin Microbiol. 1983;18(2):300-4. DOI: 10.1128/jcm.18.2.300-304.1983

63. Lai CC, Wang CY, Liu WL, Huang YT, Hsueh PR. Time to positivity of blood cultures of different Candida species causing fungaemia. J Med Microbiol. 2012;61(Pt 5):701-4. DOI: 10.1099/jmm.0.038166-0

64. Park KH, Lee MS, Lee SO, Choi SH, Sung H, Kim MN, et al. Diagnostic usefulness of differential time to positivity for catheter-related candidemia. J Clin Microbiol. 2014;52(7):2566-72. DOI: 10.1128/jcm.00605-14

65. Huang L, Zhang YY, Sun LY. Time to positivity of blood culture can predict different Candida species instead of pathogen concentration in candidemia. Eur J Clin Microbiol Infect Dis. 2013;32(7):917-22. DOI: 10.1007/s10096-013-1826-8

66. Walsh TJ, Rex JH. All catheter-related candidemia is not the same: assessment of the balance between the risks and benefits of removal of vascular catheters. Clin Infect Dis. 2002;34(5):600-2. DOI: 10.1086/338715

67. Ben-Ami R, Weinberger M, Orni-Wasserlauff R, Schwartz D, Itzhaki A, Lazarovitch T, et al. Time to blood culture positivity as a marker for catheter-related candidemia. J Clin Microbiol. 2008;46(7):2222-6. DOI: 10.1128/jcm.00214-08

68. Bouza E, Alvarado N, Alcalá L, Pérez MJ, Rincón C, Muñoz P. A randomized and prospective study of 3 procedures for the diagnosis of catheter-related bloodstream infection without catheter withdrawal. Clin Infect Dis. 2007;44(6):820-6. DOI: 10.1086/511865

69. Guembe M, Rodríguez-Créixems M, Martín-Rabadán P, Alcalá L, Muñoz P, Bouza E. The risk of catheter-related bloodstream infection after withdrawal of colonized catheters is low. Eur J Clin Microbiol Infect Dis. 2014;33(5):729-34. DOI: 10.1007/s10096-013-2004-8

70. van Eck van der Sluijs A, Oosterheert JJ, Ekkelenkamp MB, Hoepelman IM, Peters EJ. Bacteremic complications of intravascular catheter tip colonization with Gram-negative micro-organisms in patients without preceding bacteremia. Eur J Clin Microbiol Infect Dis. 2012;31(6):1027-33. DOI: 10.1007/s10096-011-1401-0

71. Pérez-Parra A, Muñoz P, Guinea J, Martín-Rabadán P, Guembe M, Bouza E. Is Candida colonization of central vascular catheters in non-candidemic, non-neutropenic patients an indication for antifungals? Intensive Care Med. 2009;35(4):707-12. DOI: 10.1007/s00134-009-1431-6

72. Rijnders BJ, Van Wijngaerden E, Peetermans WE. Catheter-tip colonization as a surrogate end point in clinical studies on catheter-related bloodstream infection: how strong is the evidence? Clin Infect Dis. 2002;35(9):1053-8. DOI: 10.1086/342905

73. López-Medrano F, Fernández-Ruiz M, Origüen J, Belarte-Tornero LC, Carazo-Medina R, Panizo-Mota F, et al. Clinical significance of Candida colonization of intravascular catheters in the absence of documented candidemia. Diagn Microbiol Infect Dis. 2012;73(2):157-61. DOI: 10.1016/j.diagmicrobio.2012.03.002

74. De Almeida BM, Breda GL, Queiroz-Telles F, Tuon FF. Positive tip culture with Candida and negative blood culture: to treat or not to treat? A systematic review with meta-analysis. Scand J Infect Dis. 2014;46(12):854-61. DOI: 10.3109/00365548.2014.952246

75. Leenders NH, Oosterheert JJ, Ekkelenkamp MB, De Lange DW, Hoepelman AI, Peters EJ. Candidemic complications in patients with intravascular catheters colonized with Candida species: an indication for preemptive antifungal therapy? Int J Infect Dis. 2011;15(7):e453-8. DOI: 10.1016/j.ijid.2011.03.009

76. Lorente L, Lecuona M, Pérez-Llombet A, González-Mesa A, Callejon M, Jiménez A, et al. Skin insertion site culture for the prediction of primary bloodstream infection. Ir J Med Sci. 2021:1-7. DOI: 10.1007/s11845-021-02685-1

77. Guembe M, Martín-Rabadán P, Echenagusia A, Camúñez F, Rodríguez-Rosales G, Simó G, et al. Value of superficial cultures for prediction of catheter-related bloodstream infection in long-term catheters: a prospective study. J Clin Microbiol. 2013;51(9):3025-30. DOI: 10.1128/jcm.01351-13

78. Aldea Mansilla C, Martínez-Alarcón J, Gracia Ahufinger I, Guembe Ramírez M. Microbiological diagnosis of catheter-related infections. Enferm Infecc Microbiol Clin (Engl Ed). 2019;37(10):668-72. DOI: 10.1016/j.eimc.2018.07.009

79. Kumar A, Sharma RM, Jaideep CN, Hazra N. Diagnosis of central venous catheter-related bloodstream infection without catheter removal: A prospective observational study. Med J Armed Forces India. 2014;70(1):17-21. DOI: 10.1016/j.mjafi.2013.08.001

80. Pérez-Granda MJ, Guembe M, Cruces R, Barrio JM, Bouza E. Assessment of central venous catheter colonization using surveillance culture of withdrawn connectors and insertion site skin. Crit Care. 2016;20:32. DOI: 10.1186/s13054-016-1201-0

81. Gowardman JR, Jeffries P, Lassig-Smith M, Stuart J, Jarrett P, Deans R, et al. A comparative assessment of two conservative methods for the diagnosis of catheter-related infection in critically ill patients. Intensive Care Med. 2013;39(1):109-16. DOI: 10.1007/s00134-012-2689-7

82. Pérez-Granda MJ, Barrio JM, Cruces R, Alonso B, Martín-Rabadán P, Collado I, et al. How should microbiology laboratories interpret

cultures of the sonicate of closed needleless connectors? Enferm Infecc Microbiol Clin (Engl Ed). 2021;39(2):72-7. DOI: 10.1016/j.eimc.2020.01.024

83. Yamin DH, Husin A, Harun A. Risk Factors of Candida parapsilosis Catheter-Related Bloodstream Infection. Front Public Health. 2021;9:631865. DOI: 10.3389/fpubh.2021.631865
84. Trofa D, Gácser A, Nosanchuk JD. Candida parapsilosis, an emerging fungal pathogen. Clin Microbiol Rev. 2008;21(4):606-25. DOI: 10.1128/cmr.00013-08
85. Rodríguez-Créixems M, Alcalá L, Muñoz P, Cercenado E, Vicente T, Bouza E. Bloodstream infections: evolution and trends in the microbiology workload, incidence, and etiology, 1985-2006. Medicine (Baltimore). 2008;87(4):234-49. DOI: 10.1097/MD.0b013e318182119b
86. Mete B, Zerdali EY, Aygun G, Saltoglu N, Balkan, II, Karaali R, et al. Change in species distribution and antifungal susceptibility of candidemias in an intensive care unit of a university hospital (10-year experience). Eur J Clin Microbiol Infect Dis. 2021;40(2):325-33. DOI: 10.1007/s10096-020-03994-6
87. Chow JK, Golan Y, Ruthazer R, Karchmer AW, Carmeli Y, Lichtenberg D, et al. Factors associated with candidemia caused by non-albicans Candida species versus Candida albicans in the intensive care unit. Clin Infect Dis. 2008;46(8):1206-13. DOI: 10.1086/529435
88. Aydin S, Derin O, Sahin M, Dinleyici R, Yilmaz M, Ceylan B, et al. Epidemiology of nosocomial candidemia, mortality and antifungal resistance, 7-year experience, in Turkey. Jpn J Infect Dis. 2022. DOI: 10.7883/yoken.JJID.2022.181
89. León C, Ruiz-Santana S, Saavedra P, Castro C, Loza A, Zakariya I, et al. Contribution of Candida biomarkers and DNA detection for the diagnosis of invasive candidiasis in ICU patients with severe abdominal conditions. Crit Care. 2016;20(1):149. DOI: 10.1186/s13054-016-1324-3
90. Bouza E, Almirante B, García Rodríguez J, Garnacho-Montero J, Salavert M, Muñoz P, et al. Biomarkers of fungal infection: Expert opinion on the current situation. Rev Esp Quimioter. 2020;33(1):1-10. DOI: 10.37201/req/2260.2019
91. Clancy CJ, Nguyen MH. Non-Culture Diagnostics for Invasive Candidiasis: Promise and Unintended Consequences. J Fungi (Basel). 2018;4(1). DOI: 10.3390/jof4010027
92. Esteves P, Lopes Lima S, Salles de Azevedo Melo A, Maria Beirão E, Nucci M, Colombo AL. (1,3)-β-D-glucan is able to predict therapeutic failure of patients with candidemia and not only mortality. Mycoses. 2021;64(3):264-71. DOI: 10.1111/myc.13224
93. Díez A, Carrano G, Bregón-Villahoz M, Cuétara MS, García-Ruiz JC, Fernandez-de-Larrinoa I, et al. Biomarkers for the diagnosis of invasive candidiasis in immunocompetent and immunocompromised patients. Diagn Microbiol Infect Dis. 2021;101(3):115509. DOI: 10.1016/j.diagmicrobio.2021.115509
94. Wang K, Luo Y, Zhang W, Xie S, Yan P, Liu Y, et al. Diagnostic value of Candida mannan antigen and anti-mannan IgG and IgM antibodies for Candida infection. Mycoses. 2020;63(2):181-8. DOI: 10.1111/myc.13035
95. Held J, Kohlberger I, Rappold E, Busse Grawitz A, Häcker G. Comparison of (1->3)-β-D-glucan, mannan/anti-mannan antibodies, and Cand-Tec Candida antigen as serum biomarkers for candidemia. J Clin Microbiol. 2013;51(4):1158-64. DOI: 10.1128/jcm.02473-12
96. Chumpitazi BF, Lebeau B, Faure-Cognet O, Hamidfar-Roy R, Timsit JF, Pavese P, et al. Characteristic and clinical relevance of Candida mannan test in the diagnosis of probable invasive candidiasis. Med Mycol. 2014;52(5):462-71. DOI: 10.1093/mmy/myu018
97. Meng Y, Kang M, Li D, Wang T, Kuang Z, Ma Y. Performance of a new Candida anti-mannan IgM and IgG assays in the diagnosis of candidemia. Rev Inst Med Trop Sao Paulo. 2020;62:e25. DOI: 10.1590/s1678-9946202062025
98. Pini P, Colombari B, Marchi E, Castagnoli A, Venturelli C, Sarti M, et al. Performance of Candida albicans germ tube antibodies (CAGTA) and its association with (1→3)-β-D-glucan (BDG) for diagnosis of invasive candidiasis (IC). Diagn Microbiol Infect Dis. 2019;93(1):39-43. DOI: 10.1016/j.diagmicrobio.2018.07.007
99. Trovato L, Astuto M, Castiglione G, Scalia G, Oliveri S. Diagnostic surveillance by Candida albicans germ tube antibody in intensive care unit patients. J Microbiol Immunol Infect. 2020;53(5):778-84. DOI: 10.1016/j.jmii.2019.02.001
100. Martínez-Jiménez MC, Muñoz P, Valerio M, Alonso R, Martos C, Guinea J, et al. Candida biomarkers in patients with candidaemia and bacteraemia. J Antimicrob Chemother. 2015;70(8):2354-61. DOI: 10.1093/jac/dkv090
101. Dichtl K, Seybold U, Wagener J. Serological biomarkers of candidemia: a retrospective evaluation of three assays. Infection. 2019;47(2):217-24. DOI: 10.1007/s15010-018-1224-3
102. Clancy CJ, Nguyen MH. Diagnosing Invasive Candidiasis. J Clin Microbiol. 2018;56(5). DOI: 10.1128/jcm.01909-17
103. Mikulska M, Giacobbe DR, Furfaro E, Mesini A, Marchese A, Del Bono V, et al. Lower sensitivity of serum (1,3)-β-d-glucan for the diagnosis of candidaemia due to Candida parapsilosis. Clin Microbiol Infect. 2016;22(7):646.e5-8. DOI: 10.1016/j.cmi.2016.05.020
104. Cuenca-Estrella M, Bassetti M, Lass-Flörl C, Rácil Z, Richardson M, Rogers TR. Detection and investigation of invasive mould disease. J Antimicrob Chemother. 2011;66 Suppl 1:i15-24. DOI: 10.1093/jac/dkq438
105. Avni T, Leibovici L, Paul M. PCR diagnosis of invasive candidiasis: systematic review and meta-analysis. J Clin Microbiol. 2011;49(2):665-70. DOI: 10.1128/jcm.01602-10
106. Chen B, Xie Y, Zhang N, Li W, Liu C, Li D, et al. Evaluation of Droplet Digital PCR Assay for the Diagnosis of Candidemia in Blood Samples. Front Microbiol. 2021;12:700008. DOI: 10.3389/fmicb.2021.700008
107. White PL, Alanio A, Brown L, Cruciani M, Hagen F, Gorton R, et al. An overview of using fungal DNA for the diagnosis of invasive mycoses. Expert Rev Mol Diagn. 2022;22(2):169-84. DOI: 10.1080/14737159.2022.2037423
108. Delaloye J, Calandra T. Invasive candidiasis as a cause of sepsis in the critically ill patient. Virulence. 2014;5(1):161-9. DOI: 10.4161/viru.26187
109. El Zakhem A, Saad H, Tayyar R, Kanj SS. Controversies in Candida management. Int J Antimicrob Agents. 2015;46 Suppl 1:S43-6. DOI: 10.1016/j.ijantimicag.2015.10.008

110. Bassetti M, Garnacho-Montero J, Calandra T, Kullberg B, Dimopoulos G, Azoulay E, et al. Intensive care medicine research agenda on invasive fungal infection in critically ill patients. Intensive Care Med. 2017;43(9):1225-38. DOI: 10.1007/s00134-017-4731-2

111. Stover KR, Kenney RM, King ST, Gross AE. Evaluation of the Use of Novel Biomarkers to Augment Antimicrobial Stewardship Program Activities. Pharmacotherapy. 2018;38(2):271-83. DOI: 10.1002/phar.2069

112. Bloos F, Held J, Schlattmann P, Brillinger N, Kurzai O, Cornely OA, et al. (1,3)-β-D-glucan-based diagnosis of invasive Candida infection versus culture-based diagnosis in patients with sepsis and with an increased risk of invasive Candida infection (CandiSep): study protocol for a randomized controlled trial. Trials. 2018;19(1):472. DOI: 10.1186/s13063-018-2868-0

113. Logan C, Martin-Loeches I, Bicanic T. Invasive candidiasis in critical care: challenges and future directions. Intensive Care Med. 2020;46(11):2001-14. DOI: 10.1007/s00134-020-06240-x

114. De Pascale G, Posteraro B, D'Arrigo S, Spinazzola G, Gaspari R, Bello G, et al. (1,3)-β-D-Glucan-based empirical antifungal interruption in suspected invasive candidiasis: a randomized trial. Crit Care. 2020;24(1):550. DOI: 10.1186/s13054-020-03265-y

115. Martínez-Jiménez MC, Muñoz P, Guinea J, Valerio M, Alonso R, Escribano P, et al. Potential role of Candida albicans germ tube antibody in the diagnosis of deep-seated candidemia. Med Mycol. 2014;52(3):270-5. DOI: 10.1093/mmy/myt025

116. Guitard J, Isnard F, Tabone MD, Antignac M, Brissot E, Senghor Y, et al. Usefulness of ß-D-glucan for diagnosis and follow-up of invasive candidiasis in onco-haematological patients. J Infect. 2018;76(5):483-8. DOI: 10.1016/j.jinf.2018.01.011

117. Agnelli C, Bouza E, Del Carmen Martínez-Jiménez M, Navarro R, Valerio M, Machado M, et al. Clinical Relevance and Prognostic Value of Persistently Negative (1,3)-β-D-Glucan in Adults With Candidemia: A 5-year Experience in a Tertiary Hospital. Clin Infect Dis. 2020;70(9):1925-32. DOI: 10.1093/cid/ciz555

118. Dobiáš R, Káňová M, Petejová N, Pisti Š K, Bocek R, Krejčí E, et al. Combined Use of Presepsin and (1,3)-β-D-glucan as Biomarkers for Diagnosing Candida Sepsis and Monitoring the Effectiveness of Treatment in Critically Ill Patients. J Fungi (Basel). 2022;8(3). DOI: 10.3390/jof8030308

119. Wei S, Wu T, Wu Y, Ming D, Zhu X. Diagnostic accuracy of Candida albicans germ tube antibody for invasive candidiasis: systematic review and meta-analysis. Diagn Microbiol Infect Dis. 2019;93(4):339-45. DOI: 10.1016/j.diagmicrobio.2018.10.017

120. Monday LM, Parraga Acosta T, Alangaden G. T2Candida for the Diagnosis and Management of Invasive Candida Infections. J Fungi (Basel). 2021;7(3). DOI: 10.3390/jof7030178

121. Beyda ND, Alam MJ, Garey KW. Comparison of the T2Dx instrument with T2Candida assay and automated blood culture in the detection of Candida species using seeded blood samples. Diagn Microbiol Infect Dis. 2013;77(4):324-6. DOI: 10.1016/j.diagmicrobio.2013.07.007

122. Steuber TD, Butler L, Sawyer A, Chappell R, Edwards J. Comparison of blood cultures versus T2 Candida Panel in management of candidemia at a large community hospital. Eur J Clin Microbiol Infect Dis. 2021;40(5):997-1001. DOI: 10.1007/s10096-020-04144-8

123. Quirino A, Scaglione V, Marascio N, Mazzitelli M, Garofalo E, Divenuto F, et al. Role of the T2Dx magnetic resonance assay in patients with suspected bloodstream infection: a single-centre real-world experience. BMC Infect Dis. 2022;22(1):113. DOI: 10.1186/s12879-022-07096-w

124. Honore PM, Redant S, Preseau T, Moorthamers S, Kaefer K, Barreto Gutierrez L, et al. T2MR can be used as a non-culture-based test together with biomarkers to improve detection of Candida in the bloodstream and reduce time delay in treating invasive candidiasis. Expert Rev Anti Infect Ther. 2022;20(3):327-9. DOI: 10.1080/14787210.2021.1964954

125. Gill CM, Kenney RM, Hencken L, Mlynarek ME, Alangaden GJ, Samuel LP, et al. T2 Candida versus beta-D-glucan to facilitate antifungal discontinuation in the intensive care unit. Diagn Microbiol Infect Dis. 2019;95(2):162-5. DOI: 10.1016/j.diagmicrobio.2019.04.016

126. Muñoz P, Vena A, Machado M, Martínez-Jiménez MC, Gioia F, Gómez E, et al. T2MR contributes to the very early diagnosis of complicated candidaemia. A prospective study. J Antimicrob Chemother. 2018;73(suppl_4):iv13-iv9. DOI: 10.1093/jac/dky048

127. Muñoz P, Vena A, Machado M, Gioia F, Martínez-Jiménez MC, Gómez E, et al. T2Candida MR as a predictor of outcome in patients with suspected invasive candidiasis starting empirical antifungal treatment: a prospective pilot study. J Antimicrob Chemother. 2018;73(suppl_4):iv6-iv12. DOI: 10.1093/jac/dky047

128. Giannella M, Pankey GA, Pascale R, Miller VM, Miller LE, Seitz T. Antimicrobial and resource utilization with T2 magnetic resonance for rapid diagnosis of bloodstream infections: systematic review with meta-analysis of controlled studies. Expert Rev Med Devices. 2021;18(5):473-82. DOI: 10.1080/17434440.2021.1919508

129. Falces-Romero I, Romero-Gómez MP, Moreno-Ramos F, Mingorance J, García-Rodríguez J, Cendejas-Bueno E. Epidemiology of bloodstream Candida species in a Spanish tertiary care hospital as a guide for implementation of T2MR (T2CANDIDA®) for rapid diagnosis of candidemia. Med Mycol. 2021;59(4):350-4. DOI: 10.1093/mmy/myaa056

130. Seitz T, Holbik J, Hind J, Gibas G, Karolyi M, Pawelka E, et al. Rapid Detection of Bacterial and Fungal Pathogens Using the T2MR versus Blood Culture in Patients with Severe COVID-19. Microbiol Spectr. 2022;10(3):e0014022. DOI: 10.1128/spectrum.00140-22

131. Hesstvedt L, Gaustad P, Andersen CT, Haarr E, Hannula R, Haukland HH, et al. Twenty-two years of candidaemia surveillance: results from a Norwegian national study. Clin Microbiol Infect. 2015;21(10):938-45. DOI: 10.1016/j.cmi.2015.06.008

132. Rajendran R, Sherry L, Deshpande A, Johnson EM, Hanson MF, Williams C, et al. A Prospective Surveillance Study of Candidaemia: Epidemiology, Risk Factors, Antifungal Treatment and Outcome in Hospitalized Patients. Front Microbiol. 2016;7:915. DOI: 10.3389/fmicb.2016.00915

133. Barchiesi F, Orsetti E, Gesuita R, Skrami E, Manso E. Epidemiology, clinical characteristics, and outcome of candidemia in a tertiary referral center in Italy from 2010 to 2014. Infection. 2016;44(2):205-

13. DOI: 10.1007/s15010-015-0845-z

134. Tedeschi S, Tumietto F, Giannella M, Bartoletti M, Cristini F, Cioni G, et al. Epidemiology and outcome of candidemia in internal medicine wards: A regional study in Italy. Eur J Intern Med. 2016;34:39-44. DOI: 10.1016/j.ejim.2016.08.020

135. Tadec L, Talarmin JP, Gastinne T, Bretonnière C, Miegeville M, Le Pape P, et al. Epidemiology, risk factor, species distribution, antifungal resistance and outcome of Candidemia at a single French hospital: a 7-year study. Mycoses. 2016;59(5):296-303. DOI: 10.1111/myc.12470

136. Toda M, Williams SR, Berkow EL, Farley MM, Harrison LH, Bonner L, et al. Population-Based Active Surveillance for Culture-Confirmed Candidemia - Four Sites, United States, 2012-2016. MMWR Surveill Summ. 2019;68(8):1-15. DOI: 10.15585/mmwr.ss6808a1

137. Medeiros MAP, Melo APV, Bento AO, Souza L, Neto FAB, Garcia JB, et al. Epidemiology and prognostic factors of nosocomial candidemia in Northeast Brazil: A six-year retrospective study. PLoS One. 2019;14(8):e0221033. DOI: 10.1371/journal.pone.0221033

138. Israel S, Amit S, Israel A, Livneh A, Nir-Paz R, Korem M. The Epidemiology and Susceptibility of Candidemia in Jerusalem, Israel. Front Cell Infect Microbiol. 2019;9:352. DOI: 10.3389/fcimb.2019.00352

139. de Oliveira CS, Colombo AL, Francisco EC, de Lima B, Gandra RF, de Carvalho MCP, et al. Clinical and epidemiological aspects of Candidemia in eight medical centers in the state of Parana, Brazil: Parana Candidemia Network. Braz J Infect Dis. 2021;25(1):101041. DOI: 10.1016/j.bjid.2020.11.006

140. ., Mirza A, Senol E, Kalkanci A. Epidemiology and Risk Factors of Candidemia Among Hospitalized Patients in a Turkish Tertiary Care Hospital. Clin Lab. 2022;68(1). DOI: 10.7754/Clin.Lab.2021.210526

141. Kayaaslan B, Eser F, Kaya Kalem A, Bilgic Z, Asilturk D, Hasanoglu I, et al. Characteristics of candidemia in COVID-19 patients; increased incidence, earlier occurrence and higher mortality rates compared to non-COVID-19 patients. Mycoses. 2021;64(9):1083-91. DOI: 10.1111/myc.13332

142. Macauley P, Epelbaum O. Epidemiology and Mycology of Candidaemia in non-oncological medical intensive care unit patients in a tertiary center in the United States: Overall analysis and comparison between non-COVID-19 and COVID-19 cases. Mycoses. 2021;64(6):634-40. DOI: 10.1111/myc.13258

143. Rajni E, Singh A, Tarai B, Jain K, Shankar R, Pawar K, et al. A High Frequency of Candida auris Blood Stream Infections in Coronavirus Disease 2019 Patients Admitted to Intensive Care Units, Northwestern India: A Case Control Study. Open Forum Infect Dis. 2021;8(12):ofab452. DOI: 10.1093/ofid/ofab452

144. Ayalon O, Cohen MJ, Orenbuch-Harroch E, Sviri S, van Heerden PV, Korem M. Invasive fungal infections in critically ill COVID-19 patients in a large tertiary university hospital in Israel. J Crit Care. 2022;69:154004. DOI: 10.1016/j.jcrc.2022.154004

145. Jia X, Li C, Cao J, Wu X, Zhang L. Clinical characteristics and predictors of mortality in patients with candidemia: a six-year retrospective study. Eur J Clin Microbiol Infect Dis. 2018;37(9):1717-24. DOI: 10.1007/s10096-018-3304-9

146. Liu F, Zhong L, Zhou F, Zheng C, Zhang K, Cai J, et al. Clinical Features, Strain Distribution, Antifungal Resistance and Prognosis of Patients with Non-albicans Candidemia: A Retrospective Observational Study. Infect Drug Resist. 2021;14:3233-46. DOI: 10.2147/idr.s323583