



## Review

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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  $\geq 65$  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	Prospective population-based	United States	In Atlanta: 14.1- 9.5		3,848 cases of candidemia 85% of the patients had a central venous catheter
	June 2008- May 2013			In Baltimore 30.9-14.4		
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 <i>C. albicans</i> was the most prevalent cause of candidiasis, followed by <i>C. glabrata</i> and <i>C.</i> <i>parapsilosis</i>

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  Period 2: March 2020– September 2020	Retrospective	Brazil	1.54  7.44	  4.76	77.8%	50% 31.2%	66.7% (30-day Mortality)	56.3% (30-day Mortality)  62.5% (30-day Mortality)	In public tertiary care hospital
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
Macaulay [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.

<b>Table 3</b> 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 <i>Candida</i> 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- $\beta$ -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 <i>Candida</i> 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	<i>C. albicans</i> 48.2% <i>C. parapsilosis</i> 33.9% <i>C. glabrata</i> 10.7% <i>C. tropicalis</i> 5.4% <i>C. guilliermondii</i> 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	<i>Candida albicans</i> 62% <i>Candida non-albicans</i> 38% <i>C. parapsilosis</i> 16.67% <i>C. glabrata</i> 12.5% <i>C. tropicalis</i> 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	<i>C. parapsilosis</i> 51.53% <i>C. albicans</i> 34.18% <i>C. glabrata</i> 6.12% <i>C. tropicalis</i> 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	<i>C. albicans</i> 41% <i>C. glabrata</i> 22% <i>C. parapsilosis</i> 16% <i>C. tropicalis</i> 9% <i>C. lusitanae</i> 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.

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