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Review

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Diagnostic and prognostic value of time to positivity in blood cultures. An opinion paper

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ABSTRACT

Time to positivity (TTP) refers to the duration required for a microbiological culture test to indicate a positive result, marking the onset of detectable bacterial or fungal growth in the sample. Numerous variables, including patient characteristics, infection source, former antimicrobial therapy, blood sample volume, and sample transportation time can influence the value of TTP. Several studies have been conducted on bloodstream infections, whereas studies on the clinical significance of yeast TTP are quite limited in the literature. Furthermore, many studies are retrospective and have a small sample size. In this opinion paper, we have formulated some questions and attempted to provide answers based on the available literature and our perspective. The objective of this opinion paper is to summarise current knowledge based on the literature, aiming to offer a critical perspective, particularly on aspects with weaker evidence, which could guide future studies in this area. We believe that TTP of blood cultures appears to exhibit considerable potential and may prove to be a valuable tool in clinical practice for estimating patient mortality risk and guiding antimicrobial therapy choices. Topics discussed include the diagnostic and prognostic role of TTP in Gram-positive and Gram-negative bacteremias and in candidemias, and the significance of differential time to positivity (DTTP). In summary, our opinion is that, based on the available literature, it is not possible to determine whether TTP provides prognostic information, particularly concerning candidemia. Therefore, clinical decisions cannot be systematically based on this parameter.

Keywords: catheter-related infections; diagnosis; microbiology; blood cultures; bacteremia; candidemia; prognosis.

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Valor diagnóstico y pronóstico del tiempo hasta la positividad en hemocultivos. Un artículo de opinión

RESUMEN

El tiempo hasta la positividad (TTP por sus siglas en inglés) se refiere a la duración necesaria para que una prueba de cultivo microbiológico indique un resultado positivo, marcando el inicio del crecimiento bacteriano o fúngico detectable en la muestra. El valor de TTP puede estar influenciado por numerosas variables, incluyendo las características del paciente, el foco de infección, el tratamiento antimicrobiano previo, el volumen de la muestra de sangre y el tiempo de transporte de la muestra.

Se han realizado varios estudios sobre infecciones en el torrente sanguíneo, mientras que los estudios sobre el significado clínico del TTP de levaduras son bastante limitados en la literatura. Además, muchos estudios son de tipo retrospectivo y de dimensión reducida. En este artículo de opinión, hemos formulado algunas preguntas e intentado proporcionar respuestas basadas en la literatura disponible y en nuestra opinión. El objetivo de este trabajo es resumir el conocimiento actual basado en la literatura, ofreciendo una perspectiva crítica, especialmente sobre aspectos con evidencia más débil, que podrían guiar futuros estudios en esta área. Creemos que TTP parece mostrar un considerable potencial y podría ser un instrumento útil en la práctica clínica para estimar el riesgo de mortalidad del paciente y guiar las decisiones sobre la terapia antimicrobiana. Los argumentos discutidos incluyen el papel diagnóstico y pronóstico de TTP en bacteriemias por Gram-positivos y Gram-negativos, en candidemias, y el significado clínico del diferencial de tiempo hasta la positividad (DTTP). En resumen, en nuestra opinión, basándonos en la literatura disponible, no es posible determinar si TTP ofrece información pronóstica, particularmente en relación con la candidemia. Por lo tanto, las decisiones clínicas no pueden basarse sistemáticamente en este parámetro.

Palabras clave: infecciones relacionadas a catéteres; diagnóstico; microbiología; hemocultivos; bacteriemia; candidemia; pronóstico.

INTRODUCTION

The time to positivity (TTP) indicates the time it takes for a blood culture to become positive, encompassing the time since loading the sample on the incubation system until the culture is flagged as positive. Since TTP can be an indirect measure of the microbial load in the blood, it could be a valuable tool in assessing the severity of the infection and guiding therapeutic decisions [1,2].

About 25 years ago, several studies were conducted on TTP, as this data is widely available in microbiology laboratories. Over the years, various blood culture incubation machines and different blood culture vials have been employed. However, TTP is underutilised in clinical practice and often is not provided to the attending physician. Currently, it is predominantly used as differential time to positivity (DTTP) for diagnosing central venous catheter-related bacteremias [3,4].

The available literature shows that TTP's diagnostic and prognostic roles in bacteremias and fungemias are conflicting. Therefore, to clarify the potential clinical impact of these data, this topic was reviewed by searching the available literature to answer the questions reported below. A search was conducted on PubMed, and all potentially relevant articles published in the last 15 years to March 2024, based on the title and abstract, were retrieved, resulting in a total of 51 articles in this opinion paper.

WHAT IS MEANT BY TTP AND DTTP IN BLOOD CULTURES?

TTP represents the duration until blood cultures show positivity. It is defined as the interval between placing blood culture bottles into the incubation machine and detecting a positive signal, indicating microbial growth. TTP may be considered an indirect measure of microbial load, assuming that the growth time is shorter when the inoculum burden is higher. However, it is important to consider that an additional time interval may occur from the moment the blood culture is collected to the introduction of the sample into the incubation machine (transportation time). This delay can be due to logistical factors related to sample transportation or the operating hours of microbiology laboratories, which are only sometimes open 24/7.

Lambregts et al. identified a discrepancy between these times, thus defining a TTP in a broad sense (from the moment of blood culture collection), which is often longer in daily clinical practice, compared to an ideal TTP, defined in a strict sense [5].

It is crucial to take into account that TTP may be influenced by various other confounding factors, including blood volume in the vials, culture conditions (such as atmosphere and broth type) and the type of sample (venipuncture or central venous catheter) [2]. The difficulty in conducting studies on this topic arises indeed from the challenge of eliminating all these factors. This often makes the data obtained difficult to apply to different hospitals (for example, those without a microbiology laboratory open 24/7).

The DTTP represents the difference in positivity time between blood cultures collected simultaneously from different sources. This parameter is utilised as an indirect measure of catheter-related bloodstream infections (CRBSI) if the difference in TTP between blood cultures collected from peripheral venipuncture and central venous catheter (CVC) is > 2 hours. Indeed, a difference > 2 h in favour of catheter-drawn blood suggests a higher bacterial load in blood cultures obtained from the CVC compared to the peripheral. This has facilitated the diagnosis of CRBSI without needing CVC removal, reducing associated costs and improving patient management [4]. However, the sensitivity and specificity of this technique appear to vary depending on the microorganism [6,7].

Conclusions: TTP is defined as the time elapsed from when the blood sample is introduced into the culture system until the detection of microbial growth. DTTP is defined as the differential time to positivity between blood cultures collected simultaneously from different sources (e.g., peripheral venipuncture and CVC). TTP and DTTP are measured in hours and minutes.

WHAT DO WE KNOW ABOUT THE TTP OF BLOOD CULTURES ISOLATING GRAM-POSITIVE BACTERIA?

Several studies have been conducted regarding the clinical use of TTP in Gram-positive bacteremias, firstly to define whether a bacteremia caused by Coagulase-negative Staphylococci (CoNS) is clinically relevant or if it should be considered a contaminant. Defining which CoNS bacteremias are truly clinically relevant could play a significant role in reducing the duration of antibiotic therapy and improving clinical outcomes, thereby reducing resistance and adverse effects associated with antibiotic therapy [8]. The main relevant studies in the literature have been summarised in Table 1 [9-11]. The available data indicate that the TTP of contaminant CoNS bacteremias may be longer compared to the TTP of clinically relevant bacteremias. In the study by Morioka *et al.*, the authors did not calculate the amount of blood in each blood culture vial, which has been associated with TTP. Additionally, the study did not account for the number of positive blood culture vials relative to the total number of collected vials [10]. As a result, the study likely did not achieve nearly 90% specificity and sensitivity for predicting CoNS bacteremia and contamination, respectively, likely due to some of the issues [12]. Furthermore, in the study by García-Vázquez et al. TTP was included in an algorithm to determine the clinical significance of CoNS bacteremia [9]. However, most of these studies are retrospective and have a small sample size.

Moreover, another aspect investigated is whether time to positivity may be correlated with an increased risk of endocarditis in patients with Gram-positive bloodstream infections (Table 2) [13-15]. In the study of Berge et al. TTP was utilised

Table 1 TTP in bacteremias by CoNS

First author, year [reference]	Type of study	Episodes/population	TTP	Conclusions
García-Vázquez et al. 2013 [9]	Retrospective, single centre An algorithm to assist in determining clinical of CoNS bacteremias was developed	269 bacteremias	-	Algorithm with best sensitivity and specificity for determining clinical significance of CoNS included TTP < 16 h[a]
Morioka et al. 2018 [10]	Retrospective, single centre	175 sets of blood cultures Oncologic patients	Bacteremia group 14 h 45 min[b] Contamination group 20 h 31 min[b]	Median TTP in bacteremia group was significantly shorter than that in their contamination group
Hitzenbichler et al. 2017 [11]	Retrospective, single centre	252 patients with NonSe-CoNS bacteremias[c]	Median TTP: - 14 h if likely infection - 16 h if possible infection - 20 h if contamination	The growth of NonSe-CoNS in the anaerobic BC bottle only and a TTP >36 h were associated with contaminations

[a]Sensitivity (62%), specificity (93%), positive predictive value 83%, negative predictive value 81%. The algorithm also included: Charlson score ≥ 3, Pitt score ≥ 1, neutropenic patients, presence of central venous catheter, identification of *Staphylococcus epidermidis*

[b]Median TTP

[c]Isolates of coagulase-negative staphylococci other than *Staphylococcus epidermidis*. Including patients from stem cell transplant units, level 1 trauma centers, and solid organ transplant centers

as a parameter in a predictive score for infective endocarditis (IE) in patients with cardiovascular implantable electronic devices (CIED) with *Staphylococcus aureus* bacteremia [15]. An ancillary study of the VIRSTA prospective cohort study confirmed similar results. TTP was independently associated with *S. aureus* IE, but the relationship between TTP and IE was not linear: extreme quartiles were associated with a higher risk of IE [13]. Furthermore, the study conducted by Oldberg *et al.* that included patients with *Enterococcus faecalis* BSI observed that a shorter TTP was associated with an increased risk of IE, suggesting the potential utility of TTP in assessing the need to perform echocardiography in patients with this condition [14].

In conclusion, the studies in the literature are limited, retrospective, and have small sample sizes, which confirms this potential use of TTP challenging. Furthermore, in *S. aureus* bacteremia, it is unclear whether the risk of IE may also be increased for longer TTP.

Conclusions: TTP could be useful in predicting whether a CoNS bacteremia has clinical significance or is a contamination. TTP could be a valuable tool in establishing the likelihood of IE in patients with Gram-positive bacteremia, influencing, along with other parameters, the decision to perform an echocardiogram. However, it is not possible to establish a definitive relationship and unique cutoffs. There is a lack of sufficient data and larger prospective studies in the literature to confirm this hypothesis, despite the potential significant impact these findings could have on clinical practice.

WHAT DO WE KNOW ABOUT THE TTP OF BLOOD CULTURES WITH ISOLATION OF GRAM-NEGATIVE BACTERIA?

Most of the available articles on the role of TTP in Gram-negative bacteremias focus on its prognostic significance, which will be discussed in the prognosis section.

The studies available in the literature have predominantly included BSIs caused by Enterobacterales and non-fermenting bacteria. In some studies, a possible relationship between TTP and the isolation of multi-drug-resistant (MDR) bacteria has emerged. In the prospective study by Puerta-Alcalde *et al.*, Gram-positive and Gram-negative BSIs in patients with febrile neutropenia were included. The study included *Escherichia coli, Klebsiella pneumoniae, Pseudomonas* spp., and MDR *Stenotrophomonas* spp. BSIs. It was found that Gram-negative bacteremias had a significantly shorter TTP compared to Gram-positive bacteremias. Interestingly, no MDR Gram-negative bacilli (GNB) bacteremias with a TTP ≥24 hours were detected [16]. These results could be significant for supporting early de-escalation stewardship strategies in this population. Also, in the retrospective study by Rolo et al., including *Pseudomonas* spp. BSIs, all MDR/ extensively drug-resistant (XDR) blood cultures were positive within the first 36 hours. This finding suggests that if blood cultures remain negative after 36 hours, it may be feasible to de-escalate treatment by excluding MDR *Pseudomonas* spp. from consideration, especially if the patient is stable [17]. Similar results were found in the prospective observational study conducted by Pan et al. It identified a signifi-

Table 2 TTP and infective endocarditis

First author, year [reference]	Type of study	Episodes/bacteria spp	TTP	Conclusions
Siméon et al. 2019 [13]	Ancillary study of the VIRSTA prospective cohort study - data from four centres	587 patients with *Staphylococcus aureus* BSI 42 definite IE	Median TTP of first positive blood culture: 13.7 h	TTP was independently associated with *S. aureus* IE[a]
Oldberg et al. 2021 [14]	Retrospective, five hospitals[b]	367 episodes of *E. faecalis* BSI in 323 patients 55 IE	Median TTP overall of 11.6 h TTP cut off of 12 h	TTP ≤ 12 h was associated with an increased risk of IE[c] There was no association between TTP and mortality
Berge et al. 2023 [15]	Retrospective cohort[d]	274 patients with a cardiac implantable electronic device (CIED) and *S. aureus* BSI 38 definite IE (including 19 with CIED IE)	TTP cut off ≤ 15 h	TTP ≤ 15 h was an independent risk factor for CIED IE and was included in the CTEPP score (TTP ≤ 15 h 4 pt)[e]

[a]The relationship between TTP and IE was not linear: extreme quartiles (TTP ≤10 h and TTP >18 h), were associated with higher risk of IE
[b]Region of Skåne in southern Sweden, served by a single microbiological laboratory that has satellite blood culture cabinets in the five largest hospitals
[c]TTP alone is a predictor of IE with sensitivity 93% and specificity 51%
[d]Laboratory databases of Clinical Microbiology of Karolinska University Hospital, Stockholm
[e]The score also included: community acquisition (2 pt), embolization (6 pt), predisposition for IE (1 pt), and positive blood cultures after start of therapy (1.5 pt). Cut off for a positive result of ≥ 2 (sensitivity 97%, specificity 25%, NPV 98%)
BSI: bloodstream infections, IE: infective endocarditis

cantly shorter TTP for Enterobacterales ESBL and *Acinetobacter baumannii* XDR than non-MDR species [18].

These results suggest that if blood cultures remain in incubation after a period of time, de-escalating antibiotic treatment could be considered, as the risk of isolating MDR organisms is reduced. This finding could help as a valuable tool in mitigating the increasing prevalence of resistant Gram-negative bacteria and improved antibiotic stewardship. However, these results are from single-centre cohorts, so they may have low external validity. They are also related to different epidemiology, as different hospitals exhibit variable epidemiology in terms of multidrug-resistant bacteria frequency and empirical antibiotic therapy usage. Additionally, there is variability in the observed cutoffs in different studies, making the application of results challenging.

Conclusions: Studies on TTP in Gram-negative bacteremias have focused on determining its prognostic value and role in identifying MDR species. MDR isolates of Enterobacterales and non-fermenting Gram-negative bacteria exhibit a shorter TTP compared to non-MDR species. However, the evidence in the literature is limited, and there is a need for larger prospective studies. If confirmed, this finding could lead to an early de-escalation of antibiotic therapy as part of antibiotic stewardship strategies.

WHAT IS THE PROGNOSTIC VALUE OF TTP IN BACTEREMIAS?

The other aspect investigated by many studies is the association between TTP and prognosis (Table 3) [1,16,17, 19-30].

Quite contrasting results have been found on the prognosis associated with TTP. In the scientific literature, there are studies that have found an association between short TTP and worse prognosis; however, other studies have shown that prolonged TTP is associated with higher mortality, and others do not have found any correlation.

The study by Hamilton et al., which included patients from a large randomised controlled trial (RAPIDO), found no association between TTP and mortality. However, the study lacked detailed information on laboratory processes. It did not consider data on the time to initiation of effective therapy (although 44% of the patients were already receiving effective treatment at the time of blood culture collection). Additionally, some bacterial isolate groups had small sample sizes, which might limit the applicability of these results to all species [31].

In contrast, the recent meta-analysis by Hsieh *et al.* has shown an apparent association between shorter TTP and worse prognosis in Gram-positive and Gram-negative BSIs [1]. This observation aligns with the understanding that a shorter time to positivity is correlated to higher bacterial load in the bloodstream, potentially contributing to a poorer clinical outcome.

Table 3 **Prognostic value of TTP in bacteremias**

First author, year [reference]	Type of study	Episodes/population	TTP	Results
Kim et al. 2010 [19]	Retrospective, single centre	684 episodes of *S. aureus* BSI / general population	Median TTP 16 h	TTP >48 h was associated with higher 30-days fatality rate
Hsu et al. 2014 [20]	Retrospective, single centre	87 patients with persistent *S. aureus* BSI[a]	Mean TTP of the first blood culture 12.6 h Mean TTP of the second 24.7 h	TTP <12 h for the first blood culture was not a risk factor for mortalitySecond TTP/first TTP ratio <1.5 was an independent risk factor for mortality
Lin et al. 2016 [21]	Retrospective, single centre	66 patients with Nontyphoidal *Salmonella* BSI	Median TTP 11.5 h Cut-off TTP 10 h	Early TTP group had greater Pittsburgh bacteremia scores, probability of ICU admission and risk of septic shock. No difference in mortality was found
Martín-Gutiérrez et al. 2017 [22]	Retrospective, single centre[b]	332 patients / 361 Gram positive and Gram-negative BSI	Median TTP 7 h 18 minTwo cut off TTP: 12 h and 27 h	Higher mortality was found in the group with the shortest TTP (<12 h) and with the longest TTP (>27 h)
Puerta-Alcalde et al. 2019 [16]	Prospective, single centre	850 BSI / onco-haematological patients with febrile neutropenia[c]	Median TTP overall 12 h No MDR-GNB was positive over 24 h	No difference was found in 30-day mortality between the group with TTP < 24 h and the remaining episodes
Chen et al. 2020 [23]	Retrospective, single center	167 patients with *E. coli* BSI/ general population	Median TTP 12.5 h Cut-off TTP was 11 h	Patients in the early TTP group had higher Pittsburgh bacteremia scores, higher incidence of septic shock and higher in-hospital mortality
Bae et al. 2021 [24]	Retrospective, single-centre[d]	1718 patients with septic shock/ Gram-positive and Gram-negative BSI	Median TTP overall 10.1 h TTP survivor and non-survivor groups (10.2 vs. 9.4 h, p = 0.35)	No significant difference between the 28-day survivors and non-survivors[e]
Paquette et al. 2021 [25]	Prospective cohort study, multicenter	315 patients with severe sepsis/ Gram-positive, Gram-negative, polymicrobial y *Candida* BSI	Median TTP overall 13 h TTP survivor and non-survivor groups (14.0 vs. 12.0 h, p = 0.69)	Shorter TTP was not associated with 90-day mortality
Rolo et al. 2022 [17]	Retrospective, single center	328 patients with *P. aeruginosa* BSI / general population	Median TTP overall 15 h Median TTP MDR/XDR 16 h No episodes of MDR/XDR with TTP >36 h	The short TTP group (≤16 h) had approximately twice the odds of mortality
Bläckberg et al., 2022 [26]	Retrospective, single center	286 episodes of *S.pyogenes* BSI/ general population	Median TTP 10.4 h	Shorter TTP was associated with 30-day mortality
Hsieh et al. 2022 [1]	Meta-analysis	Included twenty-four studies (two with episodes of *Candida* BSI)	-	Mortality was associated with the short TTP group (OR 2.98) Short TTP was a predictor of mortality and septic shock in Gram's positive and Gram's negative BSI
Bläckberg et al., 2023 [27]	Retrospective, single center	287 episodes of *S. dysgalactiae* BSI/ general population	Median TTP 9.3 h	Shorter TTP was associated with 30-day mortality

Table 3 Prognostic value of TTP in bacteremias (cont.)

Chen et al. 2023 [28]	Retrospective, single centre	101 patients with *K. pneumoniae* BSI/ age ≥ 65 years and with intra-abdominal infection	Median TTP 12.5 h	TTP was an independent risk factor for 30-day mortality
Hou et al. 2023 [29]	Retrospective, single centre	148 patients with *K. pneumoniae* BSI	Median TTP 11 hOptimal cut off for prediction of in-hospital mortality 9.4 h	Early TTP was a risk factor for in-hospital mortality only by univariate analysis No association with septic shock or ICU admission was found
Laupland et al. 2024 [30]	Retrospective cohort study including all residents of Queensland	88 314 patients with bacterial BSI (1481 patients with yeast BSI)	Median TTP overall 14 h[f]	TTP is associated with an increased risk for all-cause 30-day case fatality (the highest risk was observed in the first quartile)[g]

[a] *Staphylococcus aureus* bacteraemia persisting for >48 h
[b] Data from a prospective study
[c] The most common isolates with TTP ≥24 h were CoNS (29.9%), *Candida* spp. (22.4%), anaerobic GNB (14.9%) and *Stenotrophomonas maltophilia* (6%)
[d] Data from a prospective septic shock registry
[e] Shorter TTP showed prognostic value for predicting the 28-day mortality in the subgroups of E. coli and *Klebsiella* spp BSI
[f] 5th, 25th, 75th, and 95th percentiles of 4, 10, 20, and 53 hours, respectively
[g] Enterococci showed a decreasing risk associated with earlier quartiles of TTP
GNB: Gram-negative bacilli, BSI: bloodstream infections

Additionally, the recent multicentre study by Laupland *et al.* [30] identified an association between shorter TTP and increased mortality by retrospectively analysing data from a cohort of 88.314 patients. The study included various bacterial species: *S. aureus*, *Streptococcus pneumoniae*, pyogenic streptococci, *Pseudomonas* spp, *E. coli*, Enterobacterales, *Enterococcus*, other Gram-negatives, and anaerobes. For different bacterial species, a shorter TTP has been observed to be associated with increased mortality, although this varies by BSI aetiology. The study's main limitations include its retrospective nature, the failure to account for transportation times, and the fact that not all BSIs were confirmed, raising the possibility of including contaminants. Additionally, some parameters that can influence TTP, such as antibiotic treatment, antibiotic resistance, and patient characteristics like immunosuppression, were not considered [30].

Indeed, several confounding factors must be considered, including comorbidities, the source of bacteremia, and the promptness of antibiotic treatment initiation. Regarding antibiotic therapy, it's crucial to acknowledge that recent antibiotic treatment can reduce bacterial burden, thereby prolonging TTP. Moreover, empirical antibiotic therapy can impact prognosis and may be a confounding factor if not accounted for in the analysis. Finally, it is essential to consider the host's characteristics, as it may impact TTP: neutropenia was a predictor of short TTP, whereas pre-treatment with antibiotics appeared a predictor of prolonged TTP [32]. Despite such efforts, there may be poor external validity of the results due to variability in local epidemiology, hospital logistics, and microbiology laboratory practices. The variety demonstrates this variability of TTP results observed across different studies.

Conclusions: There is significant heterogeneity in the results obtained from the available literature, making it impossible to establish a definite association between TTP and prognosis in bacteremias. However, there appears to be a correlation between short TTP and increased mortality. Therefore, prospective multicenter studies are needed to minimise confounding factors as much as possible.

WHAT DO WE KNOW ABOUT THE TTP OF BLOOD CULTURES WITH ISOLATION OF YEASTS?

The diagnostic value of TTP in yeast bloodstream infections has been separately addressed in this opinion paper since these pathogens exhibit growth characteristics distinct from those of bacterial species. Whether the time to positivity parameter might provide clinical information about bloodstream infections caused by yeasts is not well established.

Some studies have tried to assess the clinical utility of time to positivity in candidemias, although they are fewer in number compared to those on bacteremias. Studies on TTP in *Candida* BSI are undoubtedly limited, with most being retrospective, single-centre, and having small sample sizes [1,33,34].

Table 4 TTP of bacteremias and candidemias

First author, year [reference]	Type of study	Episodes/population	TTP		Results
			Bacteremias	Candidemias	
Ning et al. 2016 [33]	Retrospective, single centre	831 bacteremias 35 candidemias	24.91 ± 22.71 h[a,b]	61.62 ± 42.77 h[a]	TTP of candidemias was longer compared to a much lower average overall TTP
Moustos et al. 2017 [38]	Retrospective, single centre	921 bacteremias 87 candidemias	92.35% Gram-negative[c] 88.12% Gram positive[c]	27.59%[c]	TTP of candidemias is longer than in bacterial BSI
Puerta-Alcalde et al. 2019 [16]	Retrospective, single centre	818 bacteremias[d] 32 candidemias[d]	TTP < 24 h in: - 449 of GNB BSI - 328 Gram positive cocci BSI	TTP < 24 h in 17 episodes	*Candida* spp and anaerobic GNB have a slow TTP
Hamilton et al. 2022 [31]	Data from a multicentre randomized controlled trial (RAPIDO)	3409 bacteremias[e] 53 candidemias[e]	Median TTP 22.7 h[b]	Median TTP 45.3 h	The longest time to positivity was observed in *Candida* spp. BSI

[a]Mean ± standard deviation
[b]TTP overall including bacteremias and candidemias
[c]Percentage of positive bottles within the first 24 hours of incubation
[d]Episodes of BSI occurring in oncological or haematological patients with febrile neutropenia
[e]Number of patients with BSI
GNB: Gram-negative bacilli, BSI: bloodstream infections

Like bacteremias, technical limitations can influence *Candida* BSI-TTP, such as sample volume, transportation time, and environmental conditions during culturing. Additionally, some studies have reported a shorter TTP for blood cultures drawn from central venous catheters. This could be attributed to a higher blood volume obtained from the CVC, but it also suggests that the source of infection could impact the duration of time to positivity [35]. Finally, like bacteremias, *Candida* BSI-TTP could be influenced by patient characteristics such as immunocompromised status, neutropenia, septic shock, and previous antifungal therapy. The duration of candidemia was often not recorded before blood samples were collected and cultured, which may also affect TTP [36,37].

Firstly, the data emerging on the relationship between *Candida* BSI-TTP and bacteremias indicate that the time to positivity in candidemias is significantly longer compared to bloodstream infections from Gram-positive and Gram-negative bacteria (Table 4) [16,31,33,38]. The variations in detection times are essential for effectively managing bloodstream infections. Recognising that *Candida* requires a more extended incubation period can impact therapeutic choices and patient care, enabling physicians to consider empirical antifungal treatments while waiting for conclusive blood culture results. Additionally, being aware of these timelines can help avoid treatment delays, enhancing outcomes for patients with candidemia.

Other studies have sought to determine whether time to positivity could be a valuable indicator for early detection of different *Candida* species. Indeed, TTP could represent a significant diagnostic tool for adjusting empirical antifungal therapy, considering the recent increase in non-*albicans Candida* species and the resulting azole resistance [39,40] (Figure 1) [36-38,41-43].

Based on the analysed studies, an interesting finding is that different *Candida* species may exhibit different growth times and, consequently, different TTP [38,43]. TTP is shorter in candidemia caused by *Candida tropicalis*, while it is significantly longer in candidemia caused by *Candida glabrata*. As suggested by some studies, this information could be important for ruling out *C. glabrata* if the TTP is short, to spare echinocandin antifungal therapy if the patient is stable [37,41,42]. However, the TTP observed in the available studies tends to be quite heterogeneous. The main issue relates to the cutoff values, which have shown considerable variation. To define a predictive cutoff for *C. glabrata* fungemia, the results obtained were TTP > 56.5 hours by Cobos-Trigueros *et al.*, >45.17 hours by Huang *et al.*, and TTP > 27.7 hours by Lai *et al.* Furthermore, results often relate to different incubation systems and types of vials, as many studies are quite dated. For these reasons, applying cutoff values to different hospital and epidemiological contexts appears challenging, with likely limited external validity of these data [44].

Concerning this matter, for instance, the study conducted by Yang et al. utilised simulated blood cultures as internal controls, yielding similar results using patient blood samples and in vitro cultures. Such an approach can be beneficial in miti-

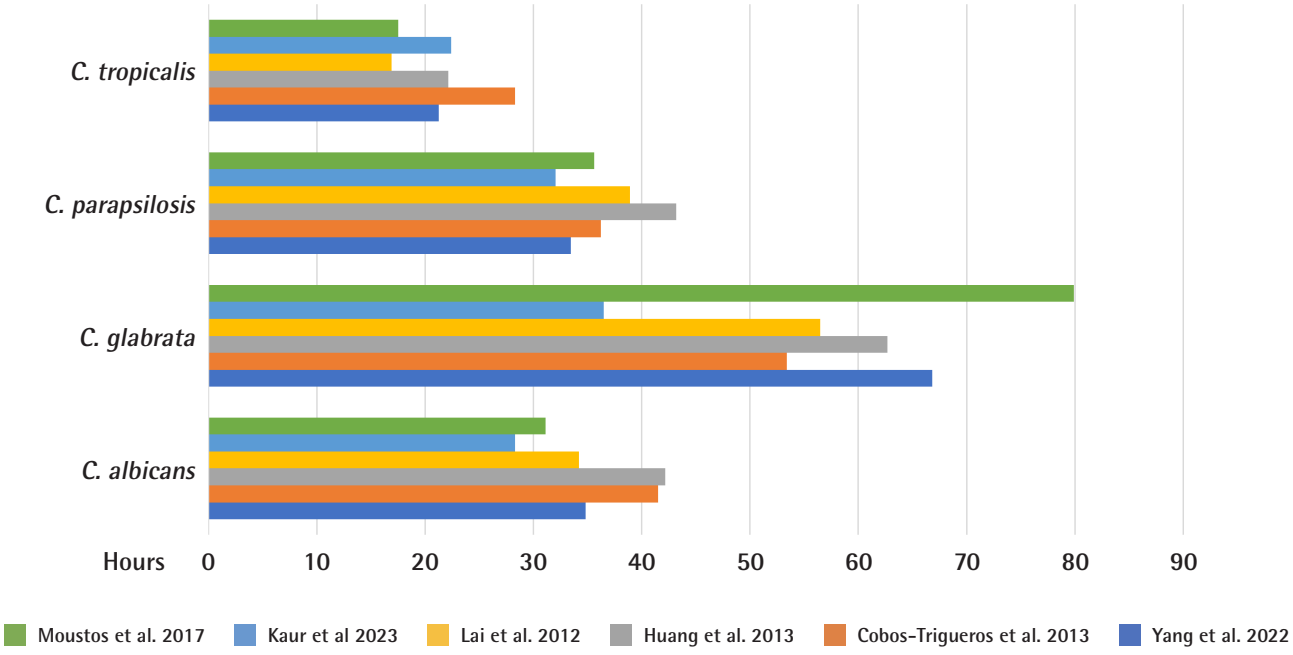

Figure 1 | Mean TTP of *Candida* species.

gating confounding factors, such as inoculation volume and transportation time, and warranting greater external validity [36].

Further research was conducted on PubMed regarding BSIs caused by non-*Candida* yeasts. Studies on TTP in BSIs caused by these pathogens are minimal. We found a series reported in the study by Nawrot et al., which considered simulated and clinical blood cultures. Seven patients had isolation in clinical blood cultures of *Sacharomyces cerevisiae* and 8 of *Cryptococcus neoformans*, the latter pertaining only to simulated fungal blood cultures [45]. Also, in the study conducted in India by Kaur *et al.*, which included adult and paediatric populations, some data on non-*Candida* yeasts are provided. Among these, the most frequently isolated was *Wickerhamomyces anomalus*, isolated exclusively from blood cultures of paediatric patients (mean TTP 31.6 h) [43]. Finally, in the large retrospective study by Laupland *et al.*, episodes of non-*Candida* yeast BSIs are included; nevertheless, a subgroup analysis specific to individual yeast species is not provided, nor are data available regarding TTP values for each species [30].

Conclusions: *Candida* species exhibit slower growth compared to bacteria, resulting in a longer time to positivity. A statistically significant difference in TTP among different *Candida* species has been observed. However, the literature has substantial heterogeneity regarding the observed TTP values, and TTP cutoff, attributable to numerous possible confounding factors. Additionally, most studies are small-scale and retrospective. Data regarding TTP values in blood cultures with non-*Candida* yeast isolates are limited to small case series in clinical studies concerning *Candida* spp. There is a lack of literature data regarding the TTP of these microorganisms.

WHAT IS THE PROGNOSTIC VALUE OF TTP IN CANDIDEMIAS?

Evidence regarding the association between time to positivity and prognosis is limited in the literature, as only a few studies have been conducted on this topic, and the results are pretty discordant (Table 5) [1,30,31,33-35,43,46]. The administered antifungal therapy and patient comorbidities could be misleading factors. However, demonstrating this correlation is relevant as it could improve clinical patient management and guide the choice of antifungal therapy.

Some studies have observed an association between shorter TTP and worse prognosis [33,35]; in others, this association is observed with longer TTP [31,34]. These findings may be attributed to different *Candida* species having pretty different growth times, making it challenging to establish a uniform result. The observed increased mortality associated with a longer TTP could be due to a greater delay in initiating appropriate antifungal therapy caused by the delay in blood culture positivity. Another explanation could be a higher prevalence of

Table 5 Prognostic value of TTP in candidemias

First author, year [reference]	Type of study	Episodes/population	TTP	Conclusions
Taur et al. 2010 [46]	Retrospective, single-center	106 episodes/ oncologic patients	32.1 hours[a]	An increase in the incubation period is significantly associated with mortality
Nunes et al. 2013 [34]	Retrospective, single-center	89 patients[b]/ general population	36 hours[c]	A longer time to positivity is associated with a higher mortality
Kim et al. 2013 [35]	Retrospective case-control, single-center	152 patients[b]	24 hours[c]	TTP ≤24 h is an independent predictor of the 6-week mortality rate
Ning et al. 2016 [33]	Retrospective, single-center	35 episodes	24 hours[c]	TTP < 24 h is associated with worse clinical outcomes
Hamilton et al. 2022 [31]	Data from a multicentre randomized controlled trial (RAPIDO)	3409 patients with bacteremias 53 candidemias	38.8 hours / 52.5 hours[d]	A slight increase in mortality is associated with a longer TTP in *Candida* BSI
Hsieh et al. 2022 [1]	Meta-analysis	Included studies conducted by Nunes et al. and Kim et al. (sample sizes of 89 and 152 patients b respectively)	Nunes et al. 36 hours[c] Kim et al. 24 hours[c]	TTP is not associated with mortality
Kaur et al. 2023 [43]	Prospective, single centre	244 patients, adults and paediatrics[b]	24 hours[c]	No significant correlation between TTP and outcome or days of hospital admission[e]
Laupland et al. 2024 [30]	Retrospective cohort study including all residents of Queensland	Of 88314 BSI there were 1481 yeast BSI	Median TTP overall 14 h[f] Median TTP yeast BSI 40 h	TTP is not associated with mortality in yeast BSI[g]

[a]Median incubation time
[b]Patients with candidemia
[c]TTP cutoff
[d]Median TTP of survivors / Median TTP of deceased (28-day mortality)
[e]A significant difference in survival was seen only among paediatric patients with *C. parapsilosis* BSI (higher mortality among the patients with TTP > 24 h)
[f]5th, 25th, 75th, and 95th percentiles of 4, 10, 20, and 53 hours, respectively.
[g]OR 0.90 (0.66 - 1.23); p = 0.50
BSI: bloodstream infections

C. glabrata among candidemias with longer TTP, which is more resistant to empirical azole therapy [46]; nevertheless, further studies are needed to confirm this finding. Indeed, the incubation period accounts for the time from blood culture collection to the start of antifungal therapy. In the study conducted by Kim et al., the total time from blood culture collection to the initiation of antifungal therapy is associated with increased mortality. However, a relationship between shorter incubation time and worse outcomes, despite early initiation of antifungal therapy, has also been observed [35], probably due to an initial higher *Candida* load in blood samples. In simulated cultures, despite increasing the inoculum concentration, no significant differences in TTP were observed by Yang *et al.* This indicates that TTP for *Candida* may be more influenced by the natural growth rate of *Candida* species rather than the inoculum concentration, at least in simulated cultures [36].

Given the retrospective nature of some studies conducted several years ago, essential data concerning the administered antifungal therapy still need to be included. For instance, in the investigation led by Kim et al., antifungal susceptibility testing was available for only 21% of the isolates [35].

The largest published study on the prognostic value of TTP in candidemia is the recent study by Laupland *et al.,* which included 1481 yeast BSIs, comprising *Candida* species and non-*Candida* yeasts such as *Cryptococcus* spp., *Rhodotorula* spp., and other yeasts. Although a relationship between TTP and mortality has been observed for most bacterial species, no association between TTP duration and mortality was found in the yeasts subgroup of patients. Additionally, precise data

on the TTP of individual species and related mortality are not available as the study was not exclusively focused on fungemias [30].

Due to the prolonged culture positivity times for *Candida* and the high mortality rates associated with *Candida* BSI, it has been necessary to develop more rapid diagnostic methodologies compared to culture-based assays. Non-culture methods, such as T2MR (T2 Magnetic Resonance), have been studied, allowing for much faster identification of *Candida* species. The T2MR method is based on molecular techniques and the use of MRI [47]. The test can identify the presence of the five most frequent *Candida* species from a blood sample in approximately five hours with a high sensitivity and specificity [48]. In addition, it appears possible to detect deep invasive candidiasis in patients with negative blood cultures. However, T2MR does not provide antifungal susceptibility data, and blood sample culture remains the only method that allows for sensitivity testing of the isolated *Candida* species. This test is costly and not widely available, especially in contexts with a low prevalence of candidemia. Further studies on TTP could have significant implications for enhancing clinical management and early detection of *Candida* species, representing a diagnostic low-cost tool available in all laboratories.

Conclusions: There is insufficient literature data to determine the prognostic value of *Candida* TTP in patients with candidemia. It would be essential to conduct prospective multicentre studies with larger sample sizes and shared protocols, leading to unique cutoffs characterised by higher external validity. Indeed, a potential clinical application of TTP in candidemias is that it could be included in clinical scores to guide the choice of antifungal therapy with possible de-escalation strategies. The potential of TTP to provide prognostic information for improved patient monitoring and more appropriate treatment remains unclear.

WHAT DO WE KNOW ABOUT BLOOD CULTURES' DTTP?

The differential time to positivity is currently mainly used in clinical practice for diagnosing central venous catheter infections when the difference in time to positivity between blood cultures obtained from peripheral venipuncture and blood cultures from the catheter is > 2 hours. However, using a 2-hour DTTP cutoff for defining a diagnosis of CR-BSI appears to have varying sensitivity depending on the microorganism isolated from blood cultures. Also, it is not valid for all microorganisms: some may require more time to be detected in the catheter sample compared to others [7,49]. Furthermore, effective use of DTTP requires careful interpretation. Since DTTP represents a difference between two TTPs, several factors related to patient characteristics, sample handling procedures, and laboratory methodologies must be considered. These elements can significantly impact the accuracy and reliability of DTTP in diagnosing CR-BSI.

For bacterial BSIs, DTTP appears to have high sensitivity and specificity in determining CR-BSI, as demonstrated by several studies that included both Gram-positive and Gram-negative bacteremias. Therefore, if the DTTP is greater than 120 minutes, it is highly likely that the BSI is associated with the central venous catheter, and thus the CVC should be removed [50-54]. However, for some bacterial species, some studies provide conflicting results. In the study by Krause et al., which included BSIs caused by *S. aureus*, the sensitivity was significantly lower and the specificity was also reduced compared to findings in other studies [55]. Similarly, the study by Orihuela-Martín et al. observed that DTTP is helpful in diagnosing CR-BSI in the presence of AmpC-producing Enterobacterales and *P. aeruginosa*. However, DTTP shows lower accuracy for Gram-positive microorganisms such as *S. aureus*, CoNS, and enterococci. Therefore, a negative result should not be considered sufficient to rule out CR-BSI caused by these latter microorganisms [56].

Regarding *Candida* bloodstream infections, there is high sensitivity but low specificity in predicting CR-BSI, supporting the notion that the reliability of DTTP in candidemia might be lower. The number of positive peripheral BCs (>=2) seems to be a more useful marker of catheter-related candidemia (sensitivity 100% in patients with three BCs) [57]. Furthermore, considering the significant difference in TTP for different *Candida* species (Figure 1), the DTTP can be deemed significant for determining CR-BSI depending on the *Candida* species. In the study by Park et al., using a DTTP cutoff of 2 hours, the sensitivity and specificity for *C. glabrata* were 77% and 50%, respectively. An optimal cutoff of 6 hours was determined for *C. glabrata*, with sensitivity and specificity of 63% and 75%, respectively. In contrast, for non-*glabrata Candida* species, the standard 2-hour cutoff yielded high sensitivity and specificity (89% and 90%, respectively) [58]. These results are likely attributable to the slower growth of *C. glabrata* compared to other species. Further studies are needed to determine whether DTTP can effectively confirm CRBSI in candidemia and whether species-specific cutoffs can be established from the standard 2 hours used for bacteremia.

Conclusions: In bacteremia, the literature suggests that a DTTP cutoff of 2 hours is generally reliable for diagnosing CRBSI. However, sensitivity and specificity may vary for different bacterial species. Concerning candidemias, the substantial variability in TTP among species probably contributes to the lack of conclusive evidence in current literature regarding the reliability of DTTP and an optimal cutoff for diagnosing CRBSI. Further studies are necessary, mainly focusing on these microorganisms, to determine if DTTP can effectively perform as a diagnostic tool and inform decisions regarding catheter removal.

OTHER UNRESOLVED ISSUES AND CHALLENGES

FOR THE FUTURE

The time to positivity is widely available in microbiology laboratories with affordable accessibility. Its clinical utilisation is extremely limited despite its potential diagnostic and prognostic value in bloodstream infections. The primary challenge in studying TTP is the presence of multiple confounding variables, and most available literature consists of small-scale retrospective studies. There appears to be a correlation between a shorter TTP and a poorer prognosis in bacteremias. However, it remains unclear whether this applies universally across all bacterial species or only to specific ones. Data on TTP in fungemias, especially non-*Candida* yeast species, are significantly limited. Study findings about candidemias are often conflicting, likely due to the distinct growth patterns of these microorganisms compared to bacterial species. Moreover, delayed diagnosis of candidemia and initiation of appropriate antifungal therapy could affect outcomes, complicating the establishment of a clear correlation between TTP and clinical outcomes.

Finally, TTP could complement other clinical scoring systems parameters to assess mortality risk, the likelihood of infective endocarditis in Gram-positive bacteremias, or the possibility of de-escalating antimicrobial therapy in stable patients.

Regarding DTTP, while a cutoff of 2 hours appears sufficiently reliable to diagnose CRBSI in bacteremias, its effectiveness as a diagnostic tool for candidemias remains unclear. Moreover, the cutoff for candidemias may need to be longer than two hours or vary among *Candida* species, given that yeast species have a longer time to positivity. There is notably limited literature available, especially concerning the use of DTTP for yeast infections.

Conclusions: Additional large-scale prospective studies are required to establish TTP's diagnostic and prognostic value in bacterial and yeast bloodstream infections. The main challenge remains in attempting to eliminate as many confounding factors as possible.

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CONFLICT OF INTEREST

Authors declare no have conflict of interest.

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