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Blood culture time-to-positivity: making use of the hidden information

B. Lamy^{1,2,3}

1) Laboratoire de Bactériologie, Hôpital L'archet 2, CHU de Nice, Nice, France

2) INSERM U1065, Centre méditerranéen de médecine moléculaire, Equipe 6, Nice, France

3) Faculté de Médecine, Université Côte d'Azur, Nice, France

Corresponding author :

Brigitte Lamy

Laboratoire de Bactériologie,

Hôpital l'Archet 2, CHU de Nice,

151 route de Saint Antoine de Ginestière,

06202 Nice

Electronic address: brigitte_lamy@yahoo.fr

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Data on time to positivity (TTP) of blood cultures is available since approx. 25 years, due to continuous monitoring blood culture instruments. It is defined as the time from the start of incubation to a positive signal. It has long been recognized to carry useful information for patient management that is progressively decrypted with varied degrees of success. First efforts have focused on early discrimination between bacterial groups or sources of infection. The TTP has then constituted the basis of the differential time to positivity method used to diagnose catheter-related bloodstream infection [1]. An increasing interest in TTP is becoming clear, highlighted by the 4-fold increase in publications on this topic over the past decade. The need to develop early de-escalation

stewardship strategies and the need for better and prompt identification of patients who should benefit from more aggressive treatment have promoted research on TTP.

Concerning the potential usefulness of TTP to guide antimicrobial therapy, most works have addressed onco-haematological patients with febrile neutropenia [2,3], likely because these patients combine high risk of antimicrobial selective pressure with high risk of bloodstream infection. In this issue, Puerta-Alcade et al. advocate, based on a retrospective study, early de-escalation at 24 hours [2] instead of 48-96 h as commonly advised because i) the great majority of episodes with positive blood culture are positive within the first 24 hours, ii) positive episodes with TTP ≥ 24 hours are commonly optimally treated infections, catheter-related infections, or infections caused by slowly growing microorganisms such as *Candida* or anaerobic Gram-negative bacteria, and iii) growth of multidrug-resistant Gram-negative bacilli is exceptional beyond 24 h. With similar logistics, other studies show short TTP in agreement with Puerta-Alcade et al's results: median TTP, although it varied between bacterial groups, was ≤ 24 h except for yeasts (e.g., [4]); most of TTPs in other patient populations were ≤ 24 h (e.g., [5]). When combined with rapid antibiotic susceptibility tests and if the laboratory is opened 24 h, this is a promising approach to speed up patient management and reduce antimicrobial selective pressure. Such approach contrasts with the "48 rule" based on tradition rather than strong evidence.

However it is important to keep in mind that TTP may be difficult to interpret and should be cautiously analysed. From a microbiological standpoint, TTP provides indirect information on the biomass, which is a function of the bacteraemia load and of the microbial growth rate: the lower the TTP (i.e., the faster the bottle shows positive), the higher is the inoculum in the blood and/or the higher the growth rate. TTP is associated with many other confounding factors usually overlooked in routine practice. Confounding factors include the volume of blood in the bottles, conditions of cultures (atmosphere, type of broth), transportation time, a concomitant antimicrobial therapy, or the type of sample (venepuncture or through a catheter). Very few studies have addressed these

points, but the study by Cobos-Trigueros et al. showed the mixed influence of logistics (transportation, laboratory opening hours), broth media, atmosphere and microorganism species on blood culture TTP of *Candida glabrata*. Among other differences, the 2 centres which participated in the study loaded bottles either round the clock or only during laboratory work hours [6]. As a likely result, the median TTP of *C. glabrata* substantially differed between the 2 centres, 56.5 h (IQR 29.7-77.3) and 83 h (IQR 46-113), respectively. Delay of bottle loading is one of the most important confounding factor because it both increases TTP (due to delay) and reduces TTP because the bacteria start to grow at room temperature. Lambregts et al. tried to take into account this point by defining TTP from the collection time (“TTP *sensu latu*”) that reflects real life better than “TTP *sensu strictu*” [3]. However, external validity is still hampered, because time to bottle load also widely varies between institutions. In other aspects, contradictory data were obtained for patients with catheter-related bloodstream infection, with either TTP < 24 h [1] or TTP > 24 h [2]. Wisely, Puerta-Alcade et al warn about difficulties in applying their threshold when organisation policies differ [2]. One should be cautious in using the cut-off values defined in single-centre studies; one should check for consistency in logistics, patient population, and technical characteristics and not forget that the cut-off values to de-escalation advocated in studies does not include time to load. Generally, time between collection and bottle loading –or time to load- needs to be precisely reported in studies on TTP as well as other confounders.

How to use TTP to predict patient outcome is less clear and requires further study [7-11]. TTP has recently been applied to predict infective endocarditis and other endovascular infections [7,12], and to predict outcome and severity of bloodstream infection[7,9,12]. TTP is an independent predictor of death (e.g., [7-11]), but interestingly, the relationship between TTP and mortality is not always linear (e.g., in *Staphylococcus aureus* bacteraemia [7,9]), and long TTP may require caution. Likely, we should focus on extreme values, not only on short TTP [7,19,11]. The distribution of TTP frequently overlap in the groups of interest, and the predictive value at the patient level is all the more reduced when the populations overlap. Again, one of the main hurdles to use TTP as an outcome predictor is

that confounders and their uncontrolled variation contribute to obscuring of the information carried in TTP. Most of the studies are retrospective studies, many of the confounding factors are not available, and virtually no study provides information on transportation time or volume of blood cultured (Table 1). As a consequence, the strength of the prediction may be altered without knowledge on the importance of the interference, and cut-off values defined in single centres may be difficult to apply elsewhere.

Regarding TTP, *Staphylococcus aureus* bacteraemia constitutes a difficult case for several reasons. First, TTP associated with *S. aureus* infective endocarditis surprisingly included both short and long TTP [6], which led the authors to assume that TTP could reflect 2 pathophysiological models for infective endocarditis (rapidly progressive infective endocarditis with high bacterial load; less virulent bacteria better controlled by the host). Confirmatory studies are required in this field. Second, short TTP (<14 h) was associated with mortality (e.g., [7]), which led the authors to recommend that patients with short TTP should be monitored more closely and be treated more aggressively. However, another study reported a higher mortality rate with long TTP [10]. Third, differential time to positivity was shown to be unreliable in accurately ruling out catheter-related bloodstream infection caused by *S. aureus* [13,14]. This important exception reflects that TTP from *S. aureus* bacteraemia is complex and presents atypical characteristics. Fourth, TTP is likely useful in monitoring patients treated for *S. aureus* bacteraemia, as failure to increase TTP by at least 50% in sequential blood culture was more frequently associated with a new focus on infection and death [15], suggesting that more aggressive treatment should be prompted with such TTPs. Fifth, TTP was advocated for distinguishing MRSA from MSSA, but the literature presents conflicting data (e.g., [7,10]).

Despite all the aforementioned limitations, TTP is promising for guidance in the management of patients. Even with important differences between the two institutions, Cobos-Trigueros et al could define a 2-step algorithm to predict *C. glabrata* bloodstream infection, reaching performance

measures of 79% (sensitivity), 90% (specificity), 59% (positive predictive value) and 96% (negative predictive value) [5]. In Puerta-Alcade et al.'s work, the frequency of positive bottles within 24 h (92.1%, [2]) and TTP variation according to pathogen groups were confirmed elsewhere (e.g., [3]), including paediatric patients with sepsis [5]. Several studies focused on specific patient groups (e.g., febrile neutropenia, sepsis in children, *S. aureus* bacteraemia, *Pseudomonas aeruginosa* bloodstream infection, *C. glabrata* infection) with similar results [2,3,5-7,10,11].

We now need external validation of thresholds and algorithms to test for robustness and transferability of the cut-off values. These algorithms would improve in performance by including microbial and clinical variables. Those proposed by Puerta et al (TTP<24 h) and by Cobos-Trigueros (a two-step algorithm) are certainly a good approach [2,6]. We also need more precise data that include data on confounding factors, such as (among others) the volume of blood cultured or the time to bottle load.

Although promising, opinions are divided on advising clinical use right now because the evidence linking TTP to patient management is not strong enough (Table 2). Full implementation in clinical practice is probably too early. The TTP has still not revealed all the hidden information it carries and ongoing efforts are desirable to establish robust cut-off and algorithms for use in clinical practice. To reach this objective, and despite difficulties to implement prospective studies in this area, evaluation should include studies on the relationship of TTP with *in vitro* speed of bacterial growth in blood culture situation, clinical trial based on TTP as a decision support tool to assess usefulness of TTP, and large multicentric prospective cohorts that record confounders. Until such studies are completed, centres who would like to implement the use of TTP for de-escalation should proceed to a local validation of the cut-off as a prerequisite.

Transparency declaration

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Table 1: Description of studies on TTP included in this article. All studies addressed only monomicrobial bacteraemia.

| Type of association assessed | Patient group | Study design | No. of patients | Preanalytic variable described, taken into account or controlled (yes/no) | | | | | | Main conclusions | Ref |
|--|---------------------------------|---------------------------------|-----------------|---|----------------------------|---------------------------------|--|-----------------------------|--------------------------|--|-----|
| | | | | Sample transportation time | Volume of blood per bottle | Culture conditions ¹ | Antimicrobial therapy at time of BC collection | Type of sample ² | Laboratory closing hours | | |
| TTP with multidrug resistant gram-negative bacilli | Onco-haematological patients | Monocentre retrospective cohort | 850 | No | No | No | Yes ³ | Yes ³ | Yes ⁴ | 92% TTP <24 h; no multidrug resistant gram-negative bacilli had a TTP >24 h. Most TTP >24 h related to <i>Candida</i> , coagulase-negative staphylococci, anaerobic bacteria | [2] |
| TTP with clinical factors | Patients with neutropenia | Monocentre unspecified study | 154 | Partly ⁵ | No | No | No | No | Yes | TTP >24h associated with central-line associated bacteraemia; 1-3% probability of bacteraemia when blood culture had remained negative for 24 h | [3] |
| TTP with Host and pathogen factors | Paediatric patients with sepsis | Multicentre prospective cohort | 562 | No | No | No | No | No | No | TTP ≤ 24 h for 88% of children | [5] |

| | | | | | | | | | | | |
|--|--|---------------------------------|------|---------------------|--------------------|-----|-----|----|------------------|--|------|
| TTP with candidemia | Patient with <i>Candida glabrata</i> candidemia | Two centre Retrospective cohort | 379 | Partly ⁵ | No | Yes | No | No | Yes | <i>C. glabrata</i> candidemia can be predicted by a TTP cut-off value which should be determined for each setting. A two-step algorithm to predict <i>C. glabrata</i> candidemia | [6] |
| TTP with infective endocarditis or death | Patients with <i>S. aureus</i> bacteraemia | Multicentre prospective cohort | 587 | No | No | No | No | No | Yes ⁴ | Early TTP associated with 30-day mortality ; U-shape distribution of infective endocarditis associated TTP | [7] |
| TTP with microbiological and clinical variables; prediction of organism of source of bacteraemia | Patients with any type of bacteraemia | Monocentre unspecified cohort | 1872 | No | No | No | Yes | No | No | Not meaningful to make prediction on the source of bacteraemia without taking into account the microorganism involved TTP ≤ 14 h predicts a <i>S. aureus</i> caused intravascular infection | [8] |
| TTP with clinical outcome | Patients with pneumococcal bacteraemic pneumonia | Monocentre prospective cohort | 278 | No | Yes ^{3,6} | No | No | No | No | Early TTP (1st quartile) associated with significant risk of invasive mechanical ventilation, longer length of stay, higher in hospital mortality, trend to higher 30-day mortality | [9] |
| TTP with adverse clinical outcome | Patients with <i>S. aureus</i> bacteraemia | Monocentre retrospective cohort | 684 | No | No | No | No | No | No | TTP>48h with the highest case-fatality rate TTP ≤ 12 and >48 h associated with increased 30-day mortality | [10] |

| | | | | | | | | | | | |
|----------------------------------|---|----------------------------------|-----|----|--------------------|----|-----|----|-----|--|------|
| TTP with in-hospital mortality | Patient with <i>Pseudomonas aeruginosa</i> bacteraemia | multicentre retrospective cohort | 74 | No | yes ^{3,6} | No | No | No | Yes | TTP ≤ 18 h associated with higher mortality | [11] |
| TTP with complicated bacteraemia | Patients with nontyphoidal salmonella bacteraemia | Monocentre retrospective cohort | 206 | No | No | No | No | No | No | TTP <10 h associated with complicated bacteraemia | [12] |
| TTP with patient outcome | Patients with <i>S. aureus</i> bacteraemia persisting for >48 h | Monocentre prospective cohort | 87 | No | yes ^{3,6} | No | Yes | No | No | second TTP/first TTP ratio of <1.5 predictor of poor outcome | [15] |

¹ atmosphere and/or type of broth

² sample obtained by venepuncture or through catheter

³ variable described but not taken into account in the statistical analysis

⁴ laboratory(ies) with a 24/24, 7/7 service only

⁵ information provided but uncontrolled variable, with resulting bias associated with laboratory closing hours

⁶ volume of blood taken into account although no information on how the volume actually cultured was checked

BC, blood culture

Table 2 : examples of advantages and shortcomings of using TTP for the purpose of antimicrobial de-escalation stewardship.

| Advantages | Shortcomings |
|---|--|
| Decision support tool to early revise antimicrobial treatment (within 24 h) | <ul style="list-style-type: none"> • Organization in the institution and in the laboratory impact TTP and consequently accuracy and robustness of the cut-off value (preanalytic and analytic variables) • susceptible to technical changes (broth composition, instrument update). Technical developments • External validation of the cut-off value required; meanwhile, cut-off value should be determined in each setting |
| Decision support tool to suspect candidemia or catheter-related bloodstream infection, with impacts on antimicrobial treatment / patient management | <ul style="list-style-type: none"> • Quality of the predictive value depends of the local recruitment • Susceptible to the presence (or not) of a concomitant antimicrobial treatment • Conflicting data in the literature for catheter-related bloodstream infection • Cut-off value should be determined in each setting (External validation required) |
| TTP can speed up de-escalating antibiotic | <ul style="list-style-type: none"> • Antibiotic de-escalation speeded up only if rapid antibiotic susceptibility tests can be applied directly from blood culture positive bottles and if laboratory is opened 24 h |