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## Unresolved issues in the epidemiology and diagnosis of bacteremia: an opinion paper

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### ABSTRACT

Bacteremia is an important cause of morbidity and mortality worldwide and, despite the diagnostic and therapeutic advances of the last decades, the evidence supporting many diagnostic aspects of bacteremia is scarce. Information on the epidemiological evolution of this entity is limited and many methodological aspects of blood culture collection and analysis are under discussion. Furthermore, the recommendations of the main scientific societies on many of these aspects are variable and, in many cases, have not been updated recently.

In this scenario, we have arranged a series of questions on different aspects of bacteremia and reviewed the literature trying to find proper answers for them. We offer our opinion on the topics where the evidence was weak.

The topics covered include epidemiological aspects of bacteremia, indications for blood culture extraction, methods for obtaining and incubating samples, or ways of transmitting results from the microbiology laboratory.

We do not intend to summarize the current clinical practice guidelines, nor will we deal with the therapeutic management of this entity. The aim of this paper is to review the current perspective on the diagnosis of bacteremia with a critical approach, to point out the gaps in the literature, to offer the opinion of a team dedicated to infectious diseases and clinical microbiology, and to identify some areas of knowledge on which future studies should focus.

**Keywords:** Bacteremia; bloodstream infection; endovascular infection; blood cultures; microbiological reporting.

### Cuestiones no resueltas en la epidemiología y el diagnóstico de la bacteriemia: un documento de opinión

### RESUMEN

La bacteriemia es una causa importante de morbilidad y mortalidad en todo el mundo y, a pesar de los avances diagnósticos y terapéuticos de las últimas décadas, la evidencia que apoya muchos aspectos diagnósticos suele ser escasa. La información sobre la evolución epidemiológica de esta entidad es limitada y muchos aspectos metodológicos sobre la obtención y análisis de hemocultivos están en discusión. Además, las recomendaciones de las principales sociedades científicas sobre muchos de estos aspectos son variables y, en muchos casos, no se han actualizado recientemente.

En este escenario, hemos preparado una serie de preguntas sobre diferentes aspectos de la bacteriemia y hemos revisado la literatura tratando de encontrar respuestas adecuadas para ellas. Ofrecemos nuestra opinión sobre los temas en los que la evidencia era débil.

Los temas tratados incluyen los aspectos epidemiológicos de la bacteriemia, las indicaciones para la extracción de hemocultivos, los métodos de obtención e incubación de muestras o las formas de transmisión de los resultados desde el laboratorio de microbiología.

No pretendemos resumir las guías de práctica clínica actuales, ni trataremos el manejo terapéutico de esta entidad. El objetivo de este trabajo es revisar la perspectiva actual sobre el diagnóstico de la bacteriemia con un enfoque crítico, señalar las carencias en la literatura, ofrecer la opinión de un equipo dedicado a las enfermedades infecciosas y a la microbiología clínica, e identificar algunas áreas de conocimiento en las que deberían centrarse futuros estudios.

**Palabras clave:** Bacteriemia, Infección del torrente circulatorio, Infección endovascular, Hemocultivos, Transmisión de resultados de microbiología.

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## INTRODUCTION

Bloodstream infection (BSI) is an entity with a high morbi-mortality worldwide. A study in Finland during 2004–2018, using data from national registries, identified a total of 173,715 BSIs with an annual incidence that increased from 150 to 309 cases/100,000 population, and a 1-month all-cause mortality rate of patients with BSI that rose from 20 to 39 deaths/100,000 population [1]. In addition, the increase of some multi-drug resistant (MDR) microorganisms causing bacteremia in recent years has become a public health concern [2].

Despite the great advances in alternative diagnostic methods of BSI in recent decades [3], blood culture remains the fundamental piece in the diagnostic approach to this entity.

However, many epidemiological and diagnostic aspects of bacteremia remain controversial. The information on the evolution of its incidence and etiology over the years is highly heterogeneous, studies show conflictive results on some key issues, and clinical guidelines offer little or no advice in some aspects of blood culture analysis.

In this scenario, we have reviewed the available literature on the diagnosis of bacteremia from a critical point of view, formulating a series of 15 questions that often arise in the evaluation of these patients. First, we analyzed the evidence about the evolution of the incidence, mortality and etiology of bacteremia. Then, we reviewed methodological aspects of blood culture analysis, including blood culture indications and various laboratory techniques, and some aspects of catheter-related bacteremia. Finally, we reviewed the information on the different methods of reporting blood cultures results from the Microbiology laboratory.

The following pages summarize the discussion and opinion on each of these questions by a team dedicated to Clinical Microbiology and Infectious Diseases.

### 1. HAS THE INCIDENCE OF BACTEREMIA CHANGED IN RECENT YEARS? HAS THE COVID-19 PANDEMIC HAD ANY IMPACT ON IT?

The incidence of bacteremia has been progressively increasing over the last 50 years, but current data do not give a clear idea of its more recent evolution. Information on the epidemiology of bacteremia in the last decade is very heterogeneous in the few population-based studies available, even more so when analyzing data at the institutional level, with numbers ranging from 101 to 309 episodes per 100,000 inhabitants/year [1,4] and between 1.3 to 15.4 episodes per 1,000 hospital admissions [5,6] (Table 1). In Spain, data ranging from 14.7 to 31.2 episodes per 1,000 admissions have been published [7, 8], and in our own institution, the mean number of bacteremic episodes has barely changed, from an average of 30.17 to 31.45 episodes per 1,000 admissions between 2002–2011 and 2012–2021, respectively (unpublished data). These numbers have not changed substantially in the last 10 years [9] with respect to data published in the previous decade [7,8,10].

Table 1 collects some of the data we have discussed [1,4–6, 1–18]. Moreover, very few studies compare the evolution with respect to previous studies in the same region or hospital [13, 19]. Therefore, there is a lack of evidence to be able to delineate a clear temporal trend in the incidence of bacteremia over the last decade.

For all these reasons, there is a need to carry out population-based studies with more recent data, studying the same regions analyzed and including the years of the pandemic, as well as to continue with institutional surveillance systems.

Information on the impact of COVID-19 on the incidence of bacteremia comes from single or multicenter cohorts. In general, low rates of bacteremia are reported in these patients, although very heterogeneous numbers ranging from 3 to 68% have been described, depending on the selected cohort [20–29]. The rate of bacteremia appears to increase in patients who have more severe disease and require ICU admission [22,23,30]. COVID-19 had a particular impact on catheter-related BSI (CR-BSI), which, after steadily decreasing in the pre-pandemic years [31–33], suffered an alarming 24% (and up to 50% in ICU) increase in incidence during the pandemic [34,35]. In our institution we observed an increase in CR-BSI from 1.89 to 5.53 episodes per 1,000 hospitalizations between 2019 and 2020 [36].

#### Conclusion:

We cannot establish that there is a clear increase or change of trend in the incidence of bacteremia in the last ten years. The COVID-19 pandemic could have caused an increase in episodes of bacteremia, fundamentally those originating in intravascular catheters.

### 2. HAS THE MORTALITY OF BACTEREMIA CHANGED IN RECENT YEARS?

Most of the available information on mortality rates has been extrapolated from multicenter cohorts, and the available population-based studies provide very disparate results (Table 1). This variability depends on multiple factors, such as the design of the studies, the population selected, the incidence of bacteremia, the causative microorganism, or the different definitions used (sepsis vs. bacteremia).

It has been estimated that mortality of patients with bacteremia reaches 250,000 deaths annually in North America and Europe combined [37]. According to the results of population-based studies published since 2010 (Table 1), the current global mortality rate for bacteremic episodes is approximately 21–32 deaths per 100,000 population, although the data are very heterogeneous [1,6,11,13,16,19]. These numbers are not very different from previous estimates [38–41].

The data are highly variable depending on the site of acquisition, with numbers ranging from 10–19% for community-onset bacteremia, to 17–28% for nosocomial-acquired episodes [6,7,11,42,43]. It reaches up to 35–50% in patients with septic shock or admitted to intensive care units [44–46].

**Table 1** Estimated incidence of bacteremia and site of acquisition, according to population-based studies published since 2010.

Reference	Period	Country	Overall incidence		Community acquired	Health-care related acquisition	Nosocomial acquisition	Mortality
			x100,000 inhabitants	x1,000 admissions				
Søgaard [11]	1992-2006	Denmark	114-166	-	45.1-53.3%	8.4-19.6%	35-38.4%	20.6-22.7% <sup>b</sup>
Wilson [12]	2004-2008	England	189	-	-	-	-	-
Skogberg [13]	2004-2007	Finland	159 (149-168)	-	-	-	-	13% <sup>b</sup> 20.8 (19.2-21.6) <sup>c</sup>
Laupland [4]	1998-2005	Canada	101.2	-	-	-	-	13% <sup>a</sup>
Nielsen [14]	2000-2008	Denmark	215.7 (198-254)	-	99 (x100,000 person-years)	50 (x100,000 person-years)	66.7 (x100,000 person-years)	-
Holmbom [6]	2000-2013	Sweden	169-265	9.4-15.4	67%	-	33%	12.8% <sup>b</sup> 10.6% CA-BSI <sup>b</sup> 17.2% HA-BSI <sup>b</sup> 142-205 <sup>d</sup>
Laupland [15]	2010-2015	Canada	117.8	-	48.6 (x100,000)	69.2 (x100,000)	-	10.6% <sup>a</sup> 12.7% HCA-BSI <sup>a</sup> 7.6% CA-BSI <sup>a</sup>
Mehl [16]	2002-2013	Norway	215	-	102 (x100,000 person-years)	85 (x100,000 person-years)	30 (x100,000 person-years)	32 <sup>c</sup>
Buetti [17]	2008-2014	Switzerland	220 (211-240)	-	-	-	-	-
Rhodes [5]	2007-2014	Thailand	110	1.3	89%	-	9.9%	-
Kontula [1]	2004-2018	Finland	216 (150-309)	-	29%	-	71%	13% <sup>b</sup> 28 <sup>c</sup>
Verway [18]	2017	Canada	150	-	17.1%	1.1%	81.8%	17% <sup>b</sup>

CA: community associated bloodstream infection. HCA: healthcare associated bloodstream infection. HA: hospital-acquired bloodstream infection. <sup>a</sup>In-hospital case fatality rate, <sup>b</sup>30-day case fatality rate, <sup>c</sup>mortality per 100,000 person-years, <sup>d</sup>mortality per 100,000 admissions.

In the case of the elderly population, a 30-day mortality rate of 22% and an annual mortality of 133 per 100,000 inhabitants have been described [47]. A 19.5% mortality rate has been estimated in nursing-home populations in a study from Spain [43].

#### Conclusion:

Bacteremia-associated mortality remains significantly high, but there is no convincing evidence of an increase in the last ten years.

### 3. HAS THE ETIOLOGY OF BACTEREMIA CHANGED IN RECENT DECADES?

*E. coli* and *S. aureus* are the most frequent microorganisms

causing bacteremia [48, 49], with the incidence of *E. coli* [9] probably being higher nowadays (Table 2). The etiology varies according to the site of acquisition, such that *S. aureus* and *P. aeruginosa* are associated with the healthcare setting, whereas *S. pneumoniae* and *E. coli* are usually associated with community onset [9,43,48].

Although, according to epidemiological surveillance programs, there seems to be an increase in bacteremias caused by Gram-negative bacilli (GNB) in general and *E. coli* in particular [48,50,51], the available information is, again, very heterogeneous [11,13,43,48,51-54]. At our institution, between 2019-2021, the incidence of Gram-positive bacteremia has been reported to range between 13.8-17.2 episodes per 1,000 admissions, compared to 18.4-19.1 episodes per 1,000 admissions for GNB (unpublished data).

Table 2		Most relevant microorganisms in bacteremia according to population-based studies published since 2010		
Reference	Period	Country	Most frequent etiology (in order of frequency)	Comment
Søgaard [11]	1992-2006	Denmark	<i>E. coli</i> <i>S. aureus</i> <i>S. pneumoniae</i>	- Significant increase in urinary and intra-abdominal infection. - Rise in <i>E. coli</i> episodes. - No change in the prevalence of Gram-positive infections.
Wilson [12]	2004-2008	England	<i>E. coli</i> (23%) CNS (16.9%) <i>S. aureus</i> (11.4%)	- <i>E. coli</i> increased by 33% during this period. - Increase in bacteremia due to GNB. - Decrease of <i>S. aureus</i> .
Skogberg [13]	2004-2007	Finland	<i>E. coli</i> (27%) <i>S. aureus</i> (13%) <i>S. pneumoniae</i> (9%)	- No significant changes in trends in Gram-positive and Gram-negative infections. - Important gender-associated differences.
Laupland [4]	1998-2005	Canada	<i>E. coli</i> (32x10 <sup>5</sup> patient-years) <i>S. aureus</i> (15.5x10 <sup>5</sup> patient-years) <i>S. pneumoniae</i> (10.2x10 <sup>5</sup> patient-years)	- Only evaluates community acquired bacteremia.
Nielsen [14]	2000-2008	Denmark	<i>E. coli</i> (28.3%) <i>S. aureus</i> (12.3%) CNS (10%) <i>S. pneumoniae</i> (9.1%)	- Decrease in CNS bacteremia. - Decrease in <i>E. coli</i> bacteremia - Increase of enterococcal bacteremia.
Holmbom [6]	2000-2013	Sweden	<i>E. coli</i> <i>S. aureus</i> CNS	- Increase of <i>E. coli</i> and <i>S.aureus</i> by 126% and 77%, respectively.
Laupland [15]	2010-2015	Canada	<i>E. coli</i> (37%) <i>S. aureus</i> (16%) <i>S. pneumoniae</i> (6%)	- Increase in bacteremias due to <i>Enterococcus</i> , <i>Pseudomonas</i> and enterobacteria other than <i>E. coli</i> - Decrease in episodes due to <i>S. viridans</i> in nosocomial acquired bacteremias.
Mehl [16]	2002-2013	Norway	<i>E. coli</i> <i>S. pneumoniae</i> <i>S. aureus</i>	- Increase in bacteremias due to GNB and <i>E. coli</i> . - Decrease in Gram-positive bacteremia.
Buetti [17]	2008-2014	Switzerland	<i>E. coli</i> <i>S. aureus</i> GNB (other than <i>E. coli</i> )	- Rise of bacteremias due to <i>E. coli</i> , GNB and enterococci. - Stable incidence of <i>S. aureus</i> .
Rhodes [5]	2007-2014	Thailand	Community-acquired: <i>E. coli</i> <i>K. pneumoniae</i> <i>Burkholderia pseudomallei</i> Hospital-acquired: <i>E. coli</i> <i>Acinetobacter</i> spp. <i>K. pneumoniae</i>	- Performed in rural areas - Frequent isolation of ESBLs in <i>E. coli</i> and <i>Acinetobacter</i> spp. - No clear trend in MRSA
Kontula [1]	2004-2018	Finland	<i>E. coli</i> (29%) <i>S. aureus</i> (13%) CNS (8%), <i>Streptococcus B-hemolyticus</i> (8%) <i>S. pneumoniae</i>	- Significant increase in the incidence of bacteremia due to <i>E. coli</i> - Low proportion of BMR bacteremia, but with an upward trend, especially due to an increase in ESBL <i>E. coli</i> .
Verway [18]	2017	Canada	<i>E. coli</i> (26.9%) <i>S. aureus</i> (15.9%) CNS (9.2%) <i>Klebsiella</i> spp.(8.2%)	- No data on antibiotic susceptibilities to differentiate the burden of susceptible from resistant pathogens.

CNS: Coagulase-negative streptococci; GNB: Gram-negative bacilli; MRSA: Methicillin-resistant *S. aureus*.

The reduction in the incidence of *S. aureus* and *S. pneumoniae* can be attributed to prevention campaigns in hospitals and to the application of pneumococcal vaccines, respectively [48].

The evidence is more robust in terms of the evolution of resistance phenotypes, highlighting a stabilization or decline in the proportion of episodes caused by resistant Gram-positive pathogens, mainly methicillin-resistant *S. aureus* (MRSA) [48, 52, 55-57], and an increase in those caused by multidrug-resistant GNB (MDR-GNB) [48]. The increase of bacteremias produced by MDR-GNB coincides with the global expansion of ESBLs [58] and carbapenemases [59], with *Klebsiella pneumoniae* being the most frequent carbapenem-resistant Gram-negative bacteria causing bacteremia [60,61], although there is considerable geographical heterogeneity in the prevalence of these enzymes.

#### Conclusion:

*E. coli* seems to be the main cause of bacteremia at present, but current data do not allow to define a clear generalized change in the trend of Gram-positive and Gram-negative episodes. There is evidence pointing to a decrease in MRSA cases and a progressive increase in MDR-GNB, with differences according to the geographical area.

#### 4. WHAT ARE THE FUNDAMENTAL INDICATIONS AND THE IDEAL TIME TO OBTAIN BLOOD CULTURES?

Although the diagnosis of bacteremia depends directly on the results of blood cultures, the information offered by guidelines regarding the indications for their extraction is very limited, with imprecise information that has not been reviewed recently [62] or without specific recommendations in this regard [63] (Table 3). Moreover, clinical variables that usually guide the indication of blood cultures, such as fever or the presence of leukocytosis, do not correctly predict

the presence of bacteremia in immunocompetent patients [64,65].

Different models that attempt to predict the presence of bacteremia have been proposed [66,67] (although they are not implemented in clinical practice nor are there currently data to evaluate their safety or cost-effectiveness [68]), as well as algorithms that propose the extraction of blood cultures according to the pretest probability of bacteremia [64,69], in an effort to obtain the maximum cost-effectiveness of the test.

In our opinion, it is not advisable to make a very restrictive use of blood cultures, given the critical importance of the diagnosis of bacteremia. Blood culture is an inexpensive, very specific and practically harmless test, patient's treatment and prognosis depend on its result, and it has epidemiological importance. We believe that the greater probability of obtaining false positive results can be overcome with a good extraction methodology, and that the associated costs are offset by the importance of the information provided by a positive result. Thus, we agree with the broader recommendations to obtain blood cultures of some societies [62,70], which also include the presence of fever, chills, hypothermia or sudden decay in neonates and the elderly or a clinical deterioration that justifies a hospital admission not justified by other causes.

The time of blood culture collection does not seem to be a decisive factor in its cost-effectiveness, which does not depend on its coincidence with fever spikes, which can occur within 1-2 hours of bacteremia [71,72]. Therefore, their extraction should not be postponed, especially in situations of sepsis. Although it is common to draw blood cultures with an arbitrary time separation of 10-30 minutes, Li et al. [73] did not observe increased performance when drawing blood cultures simultaneously or at different intervals over a 24-hour period. Unless attempting to document ongoing bacteremia for suspected endovascular infection, cultures can be drawn simultaneously [74].

Reference	Fever or hypothermia	Leukocytosis or leukopenia	Neutropenia	Clinical deterioration	Extreme ages
SEIMC [70]	Yes	Yes	No	Yes	Yes
ASM Cumitech [62]	Yes	Yes	Yes	Yes	Yes
CLSI [74]	Yes	Yes	Yes	No	No
IDSA, ASM [63]	No specific recommendations				

SEIMC: Spanish Society of Infectious Diseases and Clinical Microbiology; ASM Cumitech: American Society for Microbiology Cumitech 1C, Blood Cultures IV; IDSA, ASM: Infectious Diseases Society of America, American Society for Microbiology; CLSI: Clinical and Laboratory Standards Institute.

**Conclusion:**

The indications for obtaining blood cultures should be re-discussed and clarified by the scientific societies most concerned. We are not in favor of a restrictive use of blood cultures, nor do we believe that they should be limited to febrile episodes. Current predictive models are still based on speculation and not in the complex reality of daily clinical practice.

## 5. HOW MANY BLOOD CULTURES SHOULD BE TAKEN ROUTINELY AND WHAT VOLUME OF BLOOD SHOULD BE OBTAINED?

Assuming that a blood culture set is usually composed of two bottles per venipuncture (one for aerobic microorganisms and one for anaerobes), it is generally recommended that two to four sets be drawn, with at least 40–80mL of blood in total (i.e. 20–30mL of blood per set, with 10mL per bottle, depending on the manufacturer). Unfortunately, current guidelines are often not specific as to the volume and number of bottles that should comprise each set (Table 4) [62,63,70,74]. There is less evidence on the ideal volume to extract in the pediatric age, which depends on the age and weight of the patient [74,75].

Drawing enough volume of blood is the most important factor in improving the performance of blood cultures [76,77]. Since episodes of bacteremia have been documented with low concentrations of microorganisms (from 1–10 colony-forming units per milliliter) [78,79], there is evidence that the larger the volume of blood cultured, the higher the yield of the test [80–86], whose sensitivity can increase on the order of 3% per milliliter of cultured blood [87].

Despite its importance, it has been published that, in daily practice, up to 48% of blood cultures may have insufficient blood volume inoculated [88,89]. To determine whether sufficient volume has been drawn, visual analysis or weighing of bottles (before and after inoculation) in the laboratory [85,90] have been used, but these are tedious procedures. Therefore, tools based on different technologies have been developed to estimate the volume of cultured blood while incubating (BACTEC™ FX system, BacT/ALERT®VIRTUO™) with apparent good results [91–93]. However, these tools are currently poorly

implemented and their validity and clinical impact should be studied in depth [94].

Regarding the specific number of blood cultures, the extraction of a single set should be avoided in all cases because of its low sensitivity and potential difficulties in the interpretation of results. In a study analyzing the value of drawing three sets, the omission of the third set would result in missing up to 7.5% of bloodstream infections [95]. Therefore, in our institution, the standard of care is the extraction of three sets of blood cultures routinely. Drawing more than three sets of blood cultures is not usually necessary.

**Conclusion:**

In adults whose hemodynamic situation allows it, three sets of blood cultures should be drawn, ensuring the collection of at least 60mL of blood.

## 6. IN PATIENTS IN WHOM BLOOD CULTURES ARE TAKEN, IS THERE ANY EVIDENCE ON THE DIAGNOSTIC VALUE AND THE ABILITY TO ADVANCE THE DIAGNOSIS OF BACTEREMIA OF OTHER SAMPLES OBTAINED SIMULTANEOUSLY WITH BLOOD CULTURES?

There is practically no evidence on the simultaneous extraction of samples in parallel to blood cultures to try to predict a positive result, but it is very common to receive blood cultures and other samples in parallel in the laboratory. Since it is necessary to wait for the growth of microorganisms in blood cultures to guide antibiotic treatment, it is worth considering whether the information provided by those other biological samples could be used.

In our institution, rapid urine testing has been useful in patients with simultaneous referral of blood and urine samples to the laboratory [96]. Our data show that the presence in urine of microorganisms visible with a Gram stain doubles the possibility of having positive blood cultures in the next hours and could provide guidance on the etiology. In addition, there is evidence that in patients with bacteremic urinary tract infections in whom the same pathogen is isolated in both samples, urine culture susceptibility results correctly predict

Table 4		Recommendations on the number of blood cultures and volume of blood to be drawn in blood cultures.	
Reference	Year	Recommended volume	Recommended number of blood cultures
ASM Cumitech [62]	2005	20–30 mL per set	2–4 sets
CLSI [74]	2022	20–30 mL per set	2–3 sets
SEIMC [70]	2017	10–20 mL per set	2–4 sets
IDSA [63]	2018	20–30 mL per set	2–4 sets

ASM Cumitech: American Society for Microbiology Cumitech 1C, Blood Cultures IV; CLSI: Clinical and Laboratory Standards Institute; SEIMC: Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica; IDSA: Infectious Diseases Society of America.

blood culture results [97], allowing fast targeted antibiotic treatment. We couldn't find any studies analyzing other types of samples, which could help to identify and treat bacteremic infections sooner.

#### Conclusion:

There is a need for studies evaluating the contribution of a rapid examination of samples simultaneously submitted with blood cultures to microbiology departments.

### 7. COMPARED TO CONVENTIONAL BLOOD CULTURE IDENTIFICATION, IS THERE A POSITIVE CLINICAL IMPACT ASSOCIATED WITH THE USE OF MALDI-TOF AND OTHER RAPID TECHNIQUES?

Since the introduction of molecular and proteomic bacterial diagnostic methods, there is increasing evidence of the usefulness of these techniques. Rapid techniques (RTs) include tests such as PCR (polymerase chain reaction), MALDI-TOF MS (matrix-assisted laser desorption/ionization-time of flight mass spectrometry) or PNA-FISH (peptide nucleic acid fluorescent in

situ hybridization), which provide results in less than 2 hours. These techniques allow shortening the time needed to identify microorganisms from sample receipt compared to conventional blood culture analysis [98]. In a meta-analysis of their clinical impact [99], RTs are associated with significant decreases in mortality in the presence of an antimicrobial stewardship (AMS) team, but not in its absence. In our opinion, although they pose an important benefit, their actual clinical impact and cost-effectiveness has not yet been analyzed in depth.

MALDI-TOF systems are one of the most widespread tools in recent years. Most evidence on the clinical impact of this procedure comes from retrospective observational studies, and few studies have a prospective design or use a comparator (Table 5) [100-107]. The potential benefit of this technique, including lower mortality [101,103], is associated with the existence of an AMS team in most cases. For complex patients, such as critically ill or immunosuppressed, the evidence of efficacy for these techniques is lower [108].

The use of molecular tests, such as those based on PCR panels, have also been shown to be useful in achieving a shorter time to appropriate treatment and to guide de-escalation strategies [109,110].

**Table 5** | Studies analyzing clinical impact of MALDI-TOF with prospective design or using a comparator.

Reference	Year	Design	Result	Comment
Vlek [100]	February-April 2010	Prospective comparative study.	- Reduction of species identification time by 28.8 hours. - Increase of 11.3% in the proportion of patients with appropriate treatment.	- Does not evaluate mortality or cost-effectiveness
Huang [101]	September- November 2012	Pre-post quasi-experimental study.	- Integration of MALDI-TOF with AMS team reduces microorganism identification time and time to effective treatment. - Mortality, length of stay and recurrent bacteremia were lower in the intervention group.	- Integration with AMS team.
Clerc [102]	2010	Prospective, observational	- MALDI-TOF had an impact on 35% of Gram-negative bacteremia cases.	- Single arm. - Does not evaluate hospital stay, clinical impact or mortality.
Perez. [103]	2012-2013	Quasi-experimental study.	- Reduced time to optimal and effective treatment, shorter hospitalization time, lower mortality and estimated lower associated costs.	- Integration with AMS team.
Verroken [104]	2013-2014	Prospective comparative study with two sequential intervention periods.	- Reduced time to identification and time to optimal treatment	- Integration with AMS team.
Lockwood [105]	2014	Prospective comparative study.	- Reduced time to identification and time to optimal treatment	- Integration with AMS team.
Osthoff [106]	2014-2015	Prospective, open-label, controlled clinical trial	- Reduced treatment of contaminated blood cultures - Shorter time to active treatment and admission to ICU in intervention group	- Integration with AMS team.
O'Donnell [107]	2015	Pragmatic, controlled clinical trial	- Shorter time to definitive treatment, shorter antibiotic therapy and shorter hospital stay	- Integration with AMS team.

AMS: antimicrobial stewardship

**Conclusion:**

There is insufficient evidence on the clinical impact of routine use of MALDI-TOF and other RTs in patients with bacteremia. The benefit lies in the combination of the technique results and rapid expert information to the clinicians by a specialized team.

## 8. ARE THERE ANY AUTOMATED INCUBATION SYSTEMS FOR BLOOD CULTURES CLEARLY SUPERIOR TO OTHERS?

The introduction of automated incubation systems and continuous monitoring of blood cultures led to a significant improvement in the efficiency of these processes compared to manual methods. Currently, the most widely used systems are BacT/Alert® VIRTUO™, BD BACTEC™ FX and, to a lesser extent in Europe, VersaTREK, with some differences among them.

The only study that directly compares these three systems is by Yarbrough et al. [111], using simulations of blood cultures under standardized conditions with the same inoculum for all three systems, also comparing time to positivity (TTP) in different volumes and culture media. In this study, VIRTUO detected the main causes of bacteremia earlier, although it also showed a higher TTP for *B. fragilis* and failures in the detection of *K. kingae*.

Although most studies seem to reflect lower TTP with VIRTUO for most microorganisms [112-114], they are performed under standardized conditions, using simulations, and the results are not uniform [115].

**Conclusion:**

The clinical impact of the different automatic growth detection systems in blood cultures has not been adequately studied and their advantages and disadvantages are usually deduced from laboratory tests.

## 9. SHOULD BLOOD CULTURE INCUBATION BE MAINTAINED FOR FIVE DAYS BEFORE BEING DISCARDED?

With the evolution of automated blood culture systems, a five-day incubation period is now recommended for most commercial systems [62,74] and incubation for seven or more days is not necessary [116]. However, certain microorganisms, such as mycobacteria and dimorphic fungi, may require prolonging this period [63].

Although infective endocarditis guidelines [117,118] do not recommend a specific incubation time and suggest that detection of fastidious microorganisms, such as the HACEK group (*Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, and *Kingella*) may require prolonging this period, there is evidence that these could be detected with a five-day period with current systems [119,120]. The information on incubation time for *Bruceella* spp. is more heterogeneous [121-123], but it is currently assumed that the standard five-day period is sufficient.

The evidence is not favorable to extending the incubation period generally, although some authors propose lengthening this period in specific circumstances, such as men carrying prosthetic material at risk of *C. acnes* infection [124-126].

On the other hand, optimizing blood culture incubation time may be an important factor in avoiding unnecessary antimicrobial treatments, reducing laboratory workload, and improving antibiotic policies. In the study by Ransom et al. [127], a four-day period was sufficient to detect the vast majority of microorganisms, and only 0.11% of blood cultures were positive after four days of incubation. There is already some evidence in favor of reducing this period below five days [26,127-130], although it comes from retrospective studies using different culture systems and media, as reflected in Table 6.

**Conclusion:**

A five-day incubation period is sufficient to detect the vast majority of microorganisms, and only in individual cases should its extension be considered. In our opinion, there is insufficient data to recommend a reduction of the incubation time below five days at present.

## 10. CAN TIME TO POSITIVITY OF BLOOD CULTURES BE A PREDICTOR OF ETIOLOGY OR PROGNOSIS OF BACTEREMIA?

Time to positivity (TTP) is defined as the time from start of incubation to the detection of growth by an automated system, and it provides indirect information on the bacterial inoculum: theoretically, the higher the bacterial load, the higher the growth rate and the lower the TTP. Its main use at present is in the diagnosis of catheter-related bacteremia, and other potential uses of this determination are being investigated, as a marker of severity and predictor of the etiology of bacteremia, or to guide de-escalation treatments; but the evidence is currently contradictory and heterogeneous (Table 7).

A recent meta-analysis concludes that a short TTP is a prognostic marker associated with mortality and septic shock, applicable for most analyzed species except *Candida* spp., but it has substantial limitations [131]. Although there is evidence in favor of TTP being associated with worse prognosis in bacteremia due to *S. aureus* [132,133], *E. coli* [134], *S. pneumoniae* [135], *P. aeruginosa* [136], or *K. pneumoniae* [137], not all cases have been able to demonstrate this association between TTP and mortality [138]. Furthermore, a linear relationship is not always found, with a worse prognosis being described with both short and long TTP for *S. aureus* [139], and with long TTP for *C. albicans* [138,140].

A possible association between TTP and etiology has been described for *S. pneumoniae*, beta-hemolytic streptococci, *E. coli*, *Klebsiella* spp. and *S. aureus* [141], as well as for *P. aeruginosa* [142]. TTP has also been associated with the presence of endocarditis in cases of bacteremia by *S. aureus* [143], *E. faecalis* [144] and *A. baumannii* [145], but not by non-beta-hemolytic streptococci [146].

Table 6		Summary of a sample of studies proposing a reduction of the 5-day incubation time				
Reference	Year	Country	Design	System	Number of samples	Results and comments
Ransom [127]	2018-2019	United States	Retrospective	- BacT/Alert Virtuo (FA Plus and FN plus bottles)	158,710	- No benefit is observed in prolonging incubation longer than 4 days, including simulation with HACEK group.
Sepulveda [26]	January-March 2020	United States	Retrospective	- Bactec FX - VersaTrek	88,201	- No benefit is observed in prolonging incubation for more than 4 days, detecting 98% of microorganisms. - Conducted with a large proportion of COVID-19 patients, with a possible low proportion of bacteremia.
Bourbeau [128]	N/A (30 months)	United States	Retrospective	- BacT/Alert (FA and FN bottles)	35,500	- 3 days may be sufficient for detection of bacteria and fungi. - Use a specific type of media only.
Bourbeau [129]	N/A (18 months)	United States	Retrospective	- BacT/Alert (FAN bottles)	17,887	- 3 days may be sufficient for detection of bacteria and fungi. - Use a specific type of media only.
Doern [130]	1994-1995	United States	Retrospective	- Difco ESP	7,362	- No decrease in the detection of microorganisms is observed when decreasing to 4 days, except for <i>K. pneumoniae</i> .

Table 7		Representation of the heterogeneity of results and methodology of a selection of recent studies on the usefulness of time to blood culture positivity as a predictor of severity.		
Reference	Country	Type of study	Result	Comment
Hsieh [131]	Multinational	Meta-analysis	A short TTP was associated with higher mortality and septic shock in some bacterial species, but not in <i>Candida</i> spp.	- Notable biases, presence of heterogeneity, mixing of pediatric and adult populations, important confounding factors not assessed, meta-regression analysis not significant.
Hamilton [138]	United Kingdom	Prospective multicenter cohort study.	TTP not associated with mortality except in <i>Candida</i> spp. (elevated TTP) and possibly in streptococci.	- More methodological soundness than most studies (includes time to incubation). - Limitations: does not assess time to effective treatment, small samples in some groups.
Siméon [143],	France	Prospective multicenter cohort study.	A short TTP is related to mortality and to the presence of endocarditis in <i>S. aureus</i> bacteremia.	- Some limitations: small sample, blood culture systems used, does not analyze blood culture volume.
Kim [139]	Canada	Retrospective study	Elevated TTP is associated with mortality in <i>S. aureus</i> bacteremia.	- Some limitations: retrospective, does not have detailed clinical information, does not analyze foci of infection, does not analyze antibiotic treatment.
Oldberg [144]	Sweden	Retrospective observational study	No association was observed between TTP with mortality or the presence of endocarditis in <i>E. faecalis</i> bacteremia.	- Some limitations: retrospective study, transesophageal echocardiogram not performed in all patients, does not include patients under treatment, does not analyze blood culture volume.

TTP: time to positivity

The use of TTP has important limitations (such as different definitions of what is considered a short or long TTP) and is related to multiple confounding factors (such as the volume of blood drawn or the time between collection and start of incubation) that have not been analyzed in most studies. In

addition, variability of TTP depending on blood culture incubation systems has also been described [111]. The heterogeneity of the literature, as well as the absence of evidence on its real clinical impact, limit the use of TTP in daily clinical practice, although it is likely that it may be useful in the future.

**Conclusion:**

Currently, the use of TTP to predict severity and etiology of bacteremia is controversial, and it requires a careful evaluation.

### 11. IN WHICH CASES ARE FOLLOW-UP BLOOD CULTURES INDICATED AFTER INITIATING APPROPRIATE TREATMENT?

Follow-up blood cultures (FUBC) are recommended in cases of infective endocarditis (IE) [117,118] or endovascular infection (such as pacemaker infection, catheter infection or septic thrombophlebitis) [147], as well as candidemia [148] or bacteremia due to *S. aureus* or *S. lugdunensis*. Their extraction is also reasonable in other clinical circumstances, such as patients at high risk of endovascular infection, suspected central nervous system infection or in areas difficult to access for antimicrobials, or in the event of poor evolution despite appropriate treatment, among others.

In the case of Gram-positive microorganisms, there is evidence that justifies the extraction of FUBC in the presence of *S. aureus* bacteremia [149] due to its high virulence and capacity to produce persistent bacteremia. The same recommendations are made for *S. lugdunensis* [150]. Evidence for the rest of Gram-positives is scarce. FUBCs have limited utility in streptococcal bacteremia, and their collection should be limited in patients at low risk for deep infections, persistent bacteremia or endovascular infection [151].

The usefulness of FUBC in Gram-negative bacilli bacteremia has been evaluated in multiple studies recently [152], with very heterogeneous results. There are several cases where FUBC would have little value due to the low probability of obtaining positive cultures, which was estimated to range between 5–10.9% [153–155]. However, these studies have important limitations, including small heterogeneous populations [153,154], or assessing only episodes produced by *K. pneumoniae* [156] or bacteremias with urinary tract focus [157]. In contrast, in other studies the cost-effectiveness of FUBC reached 38.5% [158] and their collection was associated with lower mortality [158,159]. Some tools have been proposed to identify those patients with GNB bacteremia at higher risk in whom FUBC should be performed [155,159,160].

In some cases such as *Pseudomonas* spp., FUBC are usually negative if adequate focus control is obtained, but these are small series [161], and there is little evidence about their usefulness in bacteremia due to other microorganisms such as *Stenotrophomonas* or *Acinetobacter* [69].

**Conclusion:**

Follow-up blood cultures are recommended in bacteremia due to *S. aureus*, *S. lugdunensis*, and candidemia, or in cases of uncontrolled infection. In all other cases, the evidence is controversial.

### 12. IN PATIENTS WITH AN ENDOVASCULAR CATHETER AND NO CLINICAL SUSPICION OF CATHETER-RELATED BLOODSTREAM INFECTION, CAN BLOOD CULTURES BE DRAWN FROM THE CATHETER?

When obtaining blood cultures, it is recommended that blood should be drawn by direct venipuncture and extraction from the catheter should be avoided [70,77,162], unless catheter-associated infection is suspected. However, in clinical practice it is common to draw blood from the catheter in certain clinical scenarios (such as patients with poor peripheral venous access or with multiple episodes of blood collection), or to draw one set of blood cultures from the catheter and another from venipuncture, because it is a less difficult and uncomfortable process for the patient.

The recommendation not to obtain blood cultures from the catheter is based on the results of studies that point to higher false positive rates in blood cultures obtained from the catheter. In a systematic review and meta-analysis [162], all nine studies analyzed offer lower contamination rates with extraction via venipuncture.

In a systematic review of six studies [163], blood cultures obtained from the catheter have higher sensitivity and negative predictive value than those obtained by venipuncture, but also have lower specificity and positive predictive value. According to this study, out of 1,000 patients whose blood cultures are obtained from a catheter, 8 more cases of bacteremia would be detected than if they were obtained by venipuncture (103 versus 96), but 59 cases would also be incorrectly diagnosed (84 versus 25). Its higher sensitivity makes some authors consider obtaining at least one set of blood cultures from the catheter [163,164].

**Conclusion:**

Blood cultures should not be drawn from an endovascular catheter unless catheter-associated infection is suspected. Their extraction from the catheter in certain circumstances requires a very careful interpretation of results.

### 13. WHAT IS THE DIAGNOSTIC APPROACH IN PATIENTS WITH ENDOVASCULAR CATHETERS AND SUSPECTED CATHETER-RELATED BLOODSTREAM INFECTIONS (CR-BSI)?

In case of suspected CR-BSI, the latest SEIMC guidelines recommend obtaining at least two sets of blood cultures, one from peripheral venipuncture and one from the catheter, drawing blood from all lumens in case of multi-lumen catheters [165], while other guidelines do not specify this recommendation [166]. There are several studies that support obtaining blood from all catheter lumens [167,168], being equally effective the extraction from several lumens for the same culture as the extraction of a culture from each lumen [169]. In one of these studies, performed at our insti-

tution [167], if two cultures for triple-lumen catheters were eliminated, up to 37.3% of CR-BSI episodes would have been missed.

Indirect markers, such as differential time to positivity (TTP), or quantitative methods can be used to diagnose CR-BSI. Differential TTP has been implemented as the main diagnostic tool, and positivity of blood cultures obtained from a catheter 120 minutes or more apart from a culture obtained from peripheral puncture is highly suggestive of CR-BSI. The use of this cutoff point has a sensitivity and specificity of 72-96% and 90-95%, respectively [170,171]. However, there is uncertainty about its usefulness in critically ill patients [172] and in the case of certain microorganisms, such as *S. aureus* [173,174] or *Candida* spp. [175]. Therefore, the status of the host and the microorganism causing the infection must be considered, and a negative result does not exclude the diagnosis.

The reference quantitative methods are based on lysis-centrifugation procedures, being suggestive of CR-BSI if a 3-fold higher colony count is observed in the sample obtained from the catheter. Although it offers good results, it is a relatively complex and laborious technique, and it requires the sample to be processed in 20-30 minutes from blood inoculation [165], so its use is infrequent.

#### Conclusion:

If CR-BSI is suspected, blood culture collection from all catheter lumens should be taken in parallel with blood from peripheral veins. A differential TTP  $\geq 120$  minutes in blood cultures taken through the catheter lumen and peripheral veins is highly suggestive of catheter-related infection of bacterial etiology.

#### 14. SHOULD A BLOOD CULTURE REQUEST CONSTITUTE A SEPSIS ALERT?

Prompt recognition of sepsis and early use of appropriate antibiotic therapy have been shown to reduce mortality from sepsis [176]. Assuming that a request for blood cultures implies a suspicion of bacteremia and a potential septic episode, it is pertinent to ask whether the simple request for blood cultures should in itself constitute a sepsis alert in an institution.

It is noteworthy that the literature is practically non-existent regarding the potential implied value of a blood culture request in itself. Currently, both clinical guidelines and current recommendations on the implementation of the sepsis code only recommend early blood culture collection [176,177].

We are only aware of one study analyzing this aspect [178]. In this prospective study, conducted at our institution, a telephone interview from the Microbiology department after receipt of blood cultures was generally well received and was associated with better recognition of sepsis, optimization of antimicrobial treatment and lower associated costs. We observed that medical and nursing staff outside the intensive care unit tend to underestimate the presence of sepsis, even if blood cultures have been requested.

In our opinion, not only should attention be paid to a positive blood culture result, but its request alone should be considered an alert for sepsis. Further studies are needed on the appropriateness of implementing a sepsis alert from the Microbiology Department upon receipt of a simple blood culture request.

#### Conclusion:

A request for blood cultures should constitute a sepsis alert. A phone call from the Microbiology Department can contribute to the better recognition and clinical management of sepsis.

#### 15. WHAT IS THE BEST METHOD OF TRANSMITTING INFORMATION FROM THE MICROBIOLOGIST TO THE PHYSICIAN IN CHARGE OF THE PATIENT IN THE EVENT OF A POSITIVE BLOOD CULTURE RESULT?

Obtaining a positive blood culture result can have a major clinical impact. There are studies on the usefulness of the preliminary information provided by the Gram stain [179]. However, it is surprising that the best way to deliver this information has not been analyzed in depth.

In a clinical trial [180], communication of results through written reports in the patient's medical record, and oral communication at the bedside along with clinical advice, were significantly associated with a higher proportion of appropriate treatment days and lower economic costs with respect to simply issuing a report, although no associated shorter hospital stay or mortality could be demonstrated.

Although controversial and scarce, there is evidence in favor of a presential assessment by the infectious diseases specialist over a telephone assessment [181,182]. In our opinion, the person and method of transmitting blood culture results is also relevant. Although the ideal method probably involves active presential communication by an infectious disease specialist providing clinical support, studies directly comparing the clinical impact and cost-effectiveness of different procedures of communicating this information are lacking.

Given that each day of delay until definitive blood culture information is available is associated with an increase in mortality of 1.2 times per day [180], analyzing the clinical impact of different methods of transmitting information to optimize this process would influence the management of patients with bacteremia and should be considered an issue in future research.

#### Conclusion:

The limited evidence available suggests that there is a clinical benefit associated with the active communication of results of a positive blood culture, either orally or in writing, compared to only issuing a conventional report.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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