European Journal of Clinical Microbiology & Infectious Diseases (2019) 38:1435–1441
https://doi.org/10.1007/s10096-019-03568-1

ORIGINAL ARTICLE

Performance of a new combination of blood culture vials in sepsis detection: a 2-year retrospective comparison

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Received: 1 February 2019 / Accepted: 23 April 2019 / Published online: 8 May 2019

Abstract

The diagnosis of bloodstream infection requires the optimum combination of media in an automated blood culture system for maximum recovery of pathogens with the earliest time to detection. In a previous work, we showed that for patients admitted to the Emergency Department of our hospital, the combination of BACTEC lytic anaerobic and BACTEC aerobic vials was more efficient than BACTEC anaerobic and BACTEC aerobic vial. In this study, we extended the work including a broader patient population, representative of all hospital. A total of 8629 cultures were collected during the pre-lytic phase, from 01 July 2013 to 30 June 2014 and 7940 cultures during the post-lytic phase, ranged from 01 July 2015 to 30 June 2016. The number of positive blood cultures was higher during the post-lytic phase (19.74%) than in the pre-lytic phase (17.52%), particularly for *Escherichia coli*, *Staphylococcus* spp., *Enterococcus* spp., and anaerobes. We also observed a significant decreased of the time to detection, with the mean and median in the post-lytic phase of 17.68 and 13.05 h compared with 19.49 and 14.47 h in the pre-lytic phase. Whereas the time to detection was the same for organisms recovered in the aerobic Plus bottles for both time periods, time to detection for the anaerobic lytic bottles was significantly faster than with the anaerobic Plus bottles. This study carried out on a long time observation reported that a simple modification of composition of blood culture set could lead to better results in bloodstream infection detection.

Keywords Blood culture · Aerobic · Anaerobic · Lytic · BACTEC · Time to detection

Introduction

Sepsis is a worldwide threat and better tools and protocols for early diagnosis are a prerequisite for rapid and appropriate antibiotic therapy [1, 2]. There is no single laboratory test that can accurately diagnose sepsis [3]. Although blood cultures are not positive in every septic patient, this is the only test that can provide information on the etiologic agent and antimicrobial susceptibility assessing the appropriate antibiotic therapy [4]. The quality of a blood culture is measured by the time to detection of positive blood cultures, excluding contaminated blood culture sets. Improvements in the overall microbial recovery and time to results with blood cultures are realized with the introduction of automated culture systems and improvements in blood culture media. For example, Applebaum et al. [5] reported in 1983 an increased recovery of bacteria with BACTEC media supplemented with resins ("Plus" media) that bound and inactivated antibiotics, and further improvements were observed when saponin was added to media ("Lytic" media) to lyse blood cells [6, 7]. Although saponin

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10096-019-03568-1) contains supplementary material, which is available to authorized users.

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cannot be added to resin media (resins will bind and remove saponin), the combined use of resin-supplemented media and lytic media led to further improvements in recovery and earlier time to detection [8]. To evaluate the performance of the current formulations of resin and lytic media, we previously performed a prospective study comparing the performance of three BACTEC media (BACTEC Plus aerobic/F, BACTEC Plus anaerobic/F, and BACTEC lytic/10 anaerobic/F) with blood cultures collected in the Emergency Department (ED). In this ward, we observed that the combination of Plus aerobic and lytic anaerobic provided the best performance in overall recovery and time to detection [9]. In the current study, we extended the analysis including all patients in our hospital representing a broader patient population, not only those who accessed to the ED.

Material and methods

Clinical site

The Alessandria General Hospital in Italy, Piedmont, ("Santi Antonio e Biagio e C. Arrigo") is a regional healthcare hospital with 660 beds and two EDs, the first one dedicated to adults (42,000 patient admissions per year) and the second one for pediatric patients (20,000 patient admissions per year). Approximately 20% of the adult patients are admitted to the hospital and 3% of these are admitted to an Intensive Care Unit (ICU). Approximately 8000 blood cultures/year, of which around 2400 in the only ED, are performed in the Hospital, with approximately 18% of the cultures positive and 2% contaminated. Two BD BACTEC™ FX 200 (Becton, Dickinson and Company, USA) blood culture instruments are placed in the ED to eliminate delays in transporting bottles to the Microbiology Lab. Additionally, a BACTEC™ FX instrument with 400 vial capacity is placed in the Microbiology Lab. All blood culture instruments are connected to the BD EpiCenter data management system that allows remote monitoring of all vials from the central laboratory. Data obtained from the BD Epicenter database were saved into an Excel file and processed with statistical software to generate the performance information reported in this study.

Study design

In this retrospective study, we divided the time course into two phases: the 12-month pre-lytic phase from 01 July 2013 to 30 June 2014 when the blood culture sets consisted of the Plus anaerobic vial in combination with Plus aerobic vial, and the 12-month post-lytic phase from 01 July 2015 to 30 June 2016 when the sets consisted of the lytic anaerobic vial and Plus aerobic. During these two time periods, the only change in blood culture collection and processing was the use of the anaerobic blood culture vial. Samples were drawn from adult patients (> 18 years of age) with suspected sepsis and subjected to blood culture testing according to the hospital standard procedure. Each positive blood culture was processed according to standard routine procedures (Gram staining and subculture on blood agar, chocolate agar, and Schaedler agar plates at 35 °C in aerobiosis, in the presence of 5% CO_2 and in anaerobic conditions, respectively). Species identification and antimicrobial susceptibility tests of the bacterial colonies were performed using the Vitek2 XL System (bioMérieux, Marcy l'Etoile, France).

Clinical assessment

In both time periods, Weinstein criteria were followed to define a positive blood culture by a contaminated one [10]. Contaminated sets were included in the statistical analysis to assess the possible occurrence of relevant differences.

Statistical methods

Time to detection (TTD) and positivity rate (PR) were analyzed for the pre-lytic phase (BACTEC Plus aerobic/F + BACTEC Plus anaerobic/F) and post-lytic phase (BACTEC Plus aerobic/F + BACTEC lytic/10 anaerobic/F). For all positive blood cultures, the TTD was the time from incubation in the BACTEC FX instrument to the initial positive signal. Normality was assessed with a Shapiro-Wilk test. Unpaired Mann-Whitney test with one-tailed alternative hypothesis was used to compare the different TTD. The difference in TTD was analyzed for the different taxa of microorganism and statistical significance was determined when the size of each sample was greater than or equal to 10. The parametric z-test was used to compare positivity rates. To check the homogeneity of the two samples, we have compared age with a Mann-Whitney test with two-tailed alternative hypothesis, male/female ratio with a z-test for equality of proportions, and hospital location with a chi-square test. Values with a p value < 0.05 were considered significantly different. Analysis was performed with R version 3.4.2 (2017 September 28) and data were obtained from Database Epicenter™ (Becton, Dickinson and Company, USA).

Results

A total of 16,569 blood culture sets were collected during the 2-year study period: 8629 sets in the pre-lytic phase and 7940 sets in that post-lytic. The number of patients and median age were similar in the two phases, with a slight increase of male patients in the post-lytic phase. Also looking at the number of patients for each group of wards, the two periods appeared similar, except for the ED (Table 1).

Table 1 Epidemiological analysis of two periods

		Pre-lytic phase		Post-lytic phase		*p* value
Number of patients		4805		4296		
Age	Mean (sd)	66.21 (18.04)		66.58 (18.08)		0.2781
	Median	70.02		70.24		
Male (%)		55.2		57.9		0.0109
Female (%)		44.8		42.1		
Number of blood culture for group of wards						
Surgery[a]		787		527		< 0.0001
ED		1085		1327		
ICU[b]		818		620		
General medicine[c]		2115		1822		
Number of blood cultures set for group of wards						
		Total	Positive	Total	Positive	Δ Pos
Surgery		1814	280 (15.44%)	1392	221 (15.88%)	+ 0.44%
ED		2176	470 (21.65%)	2588	584 (22.56%)	+ 0.91%
ICU		752	231 (30.72%)	711	209 (29.40%)	− 1.32%
General medicine		3887	525 (13.50%)	3249	425 (13.08%)	− 0.42%
Total		8629	1506 (17.45%)	7940	1439 (18.12%)	+ 0.67%
Antibiotic doses administered (number of packs consumed)						
		357,518		329,828		

[a] Cardiac surgery, vascular surgery, thoracic surgery, neurosurgery, maxillofacial surgery, general surgery, urology surgery, otorhinolaryngology surgery, plastic surgery, prosthetic surgery, oncological surgery

[b] Unit anesthesia and resuscitation, emergency surgery, emergency therapy, emergency traumatology

[c] Geriatrics, long-term care, internal medicine, nephrology and dialysis, pulmonology, hematology, oncology, gynecology, endocrinology, cardiology, neurology, metabolic diseases, diabetology, ophthalmology, otorhinolaryngology, orthopedics, rheumatology, rehabilitation, urology, orthopedics

When compared with the total number of blood culture sets performed during the two periods, in the post-lytic phase, a small overall increase (+ 0.67%) was observed. However, differences for groups of wards were small and statistically not significant (Table 1). Extending this analysis to all wards, compared to our previous study, patients under antibiotic therapy were also included. However, for this analysis, no detailed data about interaction of lytic vial and antibiotics were available, causing difficulty in obtaining data about time of antibiotic administration and collection of blood cultures. Anyway, the antibiotic consumption was similar in both the time periods considered (Table 1).

During the study period, we observed a significant increase of positive patients during the post-lytic phase compared to the pre-lytic phase (19.74% vs. 17.52%, p value = 0.0066), while the proportion of contaminated cultures remained constant in the two periods (2.35% vs. 2.33%; Table 2).

Analyzing the data in terms of sets, a higher proportion of positive culture sets in the post-lytic phase (18.12% vs. 17.45%, p value = 0.2593) and a lower proportion of contaminated culture sets (1.34% vs. 1.69%) were observed. An increased recovery of total microorganisms was observed with the aerobic Plus/lytic anaerobic combination compared to that composed of aerobic Plus/anaerobic Plus (Table 3), especially

Table 2 Positivity recovery rate (PR) in pre-lytic phase and post-lytic phase

Analysis by patient				
Phase	Positive patients (*N*/%)	Contaminated patients (*N*/%)	Negative patients (*N*/%)	*p* value*
Pre-lytic phase	842 (17.52%)	112 (2.33%)	3841 (80.15%)	0.0066
Post-lytic phase	848 (19.74%)	101 (2.35%)	3347 (77.91%)	
Analysis by set				
Phase	Positive set (*N*/%)	Contaminated set (*N*/%)	Negative set (*N*/%)	*p* value*
Pre-lytic phase	1506 (17.45%)	146 (1.69%)	6977 (80.86%)	0.2593
Post-lytic phase	1439 (18.12%)	106 (1.34%)	6395 (80.54%)	

*Referred to PR (difference of positive patients or sets between the two phases)

Table 3 Positivity recovery (PR) in aerobic and anaerobic bottles

Microorganisms	Number of microorganisms			
	Pre-lytic phase[a]		Post-lytic phase[b]	
	Aerobic Plus	Anaerobic Plus	Aerobic Plus	Lytic anaerobic
All microorganisms	565	469	638	529
Enterobacteriaceae	231	235	289	285
Non-fermenters	56	17	44	6
Miscellaneous gram negatives	2	1	4	1
Staphylococcus spp.	166	156	189	144
Streptococcus spp.	31	29	32	35
Enterococcus spp.	24	19	36	33
Miscellaneous gram positives	6	1	7	3
Anaerobes	1	5	2	14
Yeasts	49	6	36	7

[a] 8629 specimens were processed in the pre-lytic phase

[b] 7,940 specimens were processed in the post-lytic phase

with anaerobes (Online resource 1). The overall increased RR in the post-lytic phase also should be done to increase appropriateness in the execution of blood cultures in terms of blood volume inoculated in the vials. However, this parameter was not considered during this study.

Analysis of TTD was performed on 1034 vials for the pre-lytic phase and on 1167 vials for the post-lytic phase. Due to the use of two different analytical platforms to obtain data, only for these sets the complete information about time and identification of microorganisms was available: from Siemens TD-Synergy LIS, data about identification of microorganisms were collected, while from the BD EpiCenter™ Microbiology Data Management System, data about TTD, from incubation in the instruments to positivity of vials, were obtained. Incomplete data were excluded from analysis of TTD. A significant reduction of TTD for the aerobic Plus and lytic anaerobic combination (p value < 0.0001), with the mean and median TTD in post-lytic phase 17.68 and 13.05 h compared with 19.49 and 14.47 h for the pre-lytic phase (data not shown), has been detected. The analysis of TTD was performed separately for anaerobic and aerobic vials (Table 4). Whereas the TTD was the same for microorganisms recovered in the aerobic Plus/F bottles for the two time periods, the mean and median TTD for the anaerobic lytic bottles was significantly shorter than those obtained by using the anaerobic Plus/F bottles (15.26 and 11.83 h vs. 20.65 and 15.74 h, p value < 0.0001). This was evident especially for the TTD for *Escherichia coli*, *Staphylococcus* spp., and anaerobes. Except for *E. coli*, the most recurrent microorganism, the other species have been analyzed at level of genus to allow having sufficient data to perform statistical validation. Reduction of *E. coli* TTD observed in this study was in accordance to our other study [9]. When TTD was stratified for group of wards, there was a significant reduction with lytic vials in all wards except in the ICU, particularly for ED and general medicine (Table 4).

Discussion

Several studies, even recent, have evaluated the performance of detection and TTD of principal commercial systems available, but few studies have analyzed the performance of anaerobic media without resins [11–13]. Moreover, other questions remain open: which blood culture system is most suitable for the rapid and reliable detection of important pathogens and what is the optimal combination of blood culture media [10, 14]. In fact, no one medium or system is suited for detection of all microorganisms [15]: for example, the growth of bacteria can be limited by inhibitors such as antibiotics and introduction of an antimicrobial agent-removing device made up of resins allows overcoming this limit [16]. Indeed, when compared with non-supplemented media, that media provided a better recovery of microorganisms, while reducing TTD [6, 17–22]. Other improvements in media efficiency were observed with the introduction of saponin-supplemented BACTEC lytic media [8]. A recent study in simulated conditions shows that lytic medium has a significantly better detection rate and shorter TTD compared to other three types of anaerobic vial without resins [23]. However, the current formulations of lytic and resin media and the current generation BACTEC system had not been evaluated until our recent work that focused on blood cultures performed with patients in the Emergency Department [9]. We observed a significant improvement in time to detection and overall recovery with the BACTEC lytic anaerobic media. However, the results of this

Table 4 Time to detection (TTD) of positive cultures

TTD for microorganisms	Blood culture vial	Pre-lytic phase Mean (sd)[a]	Median[a]	Post-lytic phase Mean (sd)[a]	Median[a]	*p* value
All microorganisms	AN vials	20.65 (17.28)	15.74	15.26 (11.49)	11.83	< 0.0001
	AE vials	19.11 (16.35)	14.23	19.63 (16.90)	15.10	0.8156
Enterobacteriaceae	AN vials	16.72 (16.22)	11.92	12.67 (10.71)	10.44	< 0.0001
	AE vials	14.19 (11.52)	11.39	16.83 (17.27)	11.79	0.9297
E.coli	AN vials	16.69 (17.26)	11.39	11.92 (9.70)	10.28	0.0117
	AE vials	12.86 (8.62)	10.92	15.39 (15.65)	11.18	0.7914
Other	AN vials	16.75 (15.13)	12.47	13.64 (11.87)	11.42	0.3025
	AE vials	15.46 (13.65)	11.84	18.72 (19.08)	12.82	0.9362
Non-fermenters	AN vials	27.92 (20.76)	20.38	17.71 (7.32)	19.53	NA[d]
	AE vials	19.40 (17.79)	15.99	18.76 (9.43)	18.13	0.9242
Miscellaneous genera[b]	AN vials	36.30 (NA)	36.30	22.28 (2.19)	22.28	NA[d]
	AE vials	42.85 (14.27)	42.85	10.61 (1.94)	11.07	NA[d]
Staphylococcus spp.	AN vials	25.65 (15.89)	22.12	18.84 (9.66)	17.45	<0.0001
	AE vials	21.86 (16.02)	17.99	21.62 (12.34)	19.34	0.8423
Streptococcus spp.	AN vials	15.39 (7.09)	13.82	15.26 (12.11)	12.07	0.0850
	AE vials	15.75 (8.85)	12.72	15.81 (11.49)	11.89	0.2119
Enterococcus spp.	AN vials	16.56 (20.54)	13.73	13.24 (7.76)	11.59	0.4254
	AE vials	11.95 (5.33)	12.28	14.43 (6.84)	12.79	0.8716
Miscellaneous genera[d]	AN vials	64.79 (NA)	64.79	33.47 (26.17)	18.67	NA[d]
	AE vials	38.00 (24.76)	30.56	27.85 (13.05)	25.56	NA[d]
Anaerobes	AN vials	52.85 (38.83)	37.93	25.39 (22.58)	19.81	NA[d]
	AE vials	17.88 (NA)	17.88	72.29 (71.31)	72.29	NA[d]
Candida spp.	AN vials	25.21 (5.85)	23.74	24.54 (15.96)	26.64	NA[d]
	AE vials	34.84 (25.23)	28.27	38.28 (28.62)	25.41	0.6539
TTD for group of wards	Blood culture vial	Pre-lytic phase Mean (sd)[a]	Median[a]	Post-lytic phase Mean (sd)[a]	Median[a]	*p* value
Surgery	AN vials	19.47 (15.87)	16.19	15.21 (11.26)	11.92	0.0456
	AE vials	22.34 (22.09)	15.47	21.53 (14.89)	17.12	0.9560
ED	AN vials	19.13 (14.65)	14.05	14.65 (8.85)	11.77	< 0.0001
	AE vials	16.06 (13.10)	12.56	20.09 (17.64)	15.15	0.9957
ICU	AN vials	22.00 (16.75)	17.74	20.78 (16.41)	14.62	0.2150
	AE vials	21.08 (13.24)	16.07	22.99 (17.85)	18.26	0.6756
General medicine	AN vials	22.35 (20.36)	16.78	14.36 (12.38)	10.62	< 0.0001
	AE vials	19.26 (16.12)	14.55	17.44 (16.33)	12.93	0.0433

[a] In hours

[b] *Haemophilus*, *Pasteurella*, *Moraxella*, *Neisseria*

[c] *Aerococcus*, *Listeria*, *Corynebacterium*

[d] Insufficient number of isolates for statistical analysis

study were not broadly applicable because relatively few patients were receiving antibiotics at the time of blood culture collection and critically ill patients such as those in an ICU were not considered. For this reason, we extended our initial study to include two consecutive 1-year periods for the entire hospital population. In the two phases, the only difference was the composition of blood culture set: while in the pre-lytic phase, the combination of aerobic and anaerobic resin vials was used; the post-lytic phase consisted the combined use of the aerobic resin and anaerobic lytic vials. The results obtained were consistent with our previous study, with significantly more positive cultures and decreased time to results (Tables 2, 3, and 4; Online Resources 1 and 2). The overall positivity rate increased from 17.52 to 19.74% for the new combination (Table 2); more in detail, we detected a higher number of Enterobacteriaceae, *Staphylococcus* spp., *Enterococcus* spp., anaerobes, and total microorganisms recovered with the aerobic Plus/lytic anaerobic vials compared

to those recovered by aerobic Plus/anaerobic Plus vials (Table 3). Detailed data of RR for each species were summarized in the Online Resources 1 and 2: data were resumed for blood culture, not for set.

Additionally, the mean and median TTD improved from 19.49 and 14.47 h to 17.68 and 13.05 h.

The most significant improvements in TTD were observed with *E. coli*, *Staphylococcus* spp., and anaerobes (Tables 3 and 4).

Overall, results of our study are consistent with those of our previous study performed on Emergency Department patients, and support use of the combination of the aerobic resin media with the lytic anaerobic media. The resin media offer the advantage of inactivation of the inhibitory effects of antibiotics while the lytic media improve both recovery of microorganisms and reduce the time to detection through lyses of blood cells that enrich the nutrient quality of the media and reduce the metabolic activity of non-microbial cells. The current study overcomes the limitations of our previous work: data were obtained from all wards and not only by the ED. Moreover, the patient population was representative of a broader range of different hospital wards. However, while in our previous study with a limited number of patients receiving antibiotic, we reported similar recovery in the anaerobic Plus vial and lytic anaerobic vial; one limitation of this study is the inability to precisely identify which patients were under antibiotic therapy at the time of venipuncture for blood culture. For this reason, influence of antibiotic therapy on recovery of lytic vial could not be suitably evaluated. Another limit was the absence of analysis for single species and in correlation with the main antibiotic resistance mechanisms (mecA, KPC, Van A/B). In order to perform a statistically significant analysis, this study focused on an overall comparison of the RR and TTD for the two combinations of vials, in relation to groups of wards and group of microorganisms. Further observations need to be performed at level of microorganisms' species and in correlation with different clinical pictures of the patients. Finally, this study was limited to adult patients: care should be taken to not extrapolate the findings herein to pediatric populations.

Author contributions PB collected data, prepared the data set, and was a major contributor in writing the manuscript. FR analyzed the data set and created tables. AR and EG supervised and coordinated team work and contributed in writing the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest Becton, Dickinson and Company (BD) provided non-financial support to the publication of manuscript.

Ethical approval For this type of study, formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

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