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ORIGINAL ARTICLE

Recovery and time to growth of isolates in blood culture bottles: Comparison of BD Bactec Plus Aerobic/F and BD Bactec Plus Anaerobic/F bottles

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Abstract

Background: This study was done to compare the growth of pathogens in paired aerobic/anaerobic blood culture bottles versus the use of only aerobic bottles, and to analyze the time to growth in both atmospheres. *Methods:* We retrospectively evaluated the results of all blood cultures collected over a 2-y period for the diagnosis of central venous catheter-related bloodstream infections or other severe infections in oncology patients. *Results:* Among the 487 isolates, 174 (35.7%), all aerobic, grew only in the aerobic bottle; 250 (51.3%), all aerobic, grew in both bottles; and 63 (12.9%) grew only in the anaerobic bottle, of which 24 were anaerobic and 39 were aerobic microorganisms (8% of positive blood cultures). Of these 39 aerobic microorganisms, 12 were Gram-negative, 17 staphylococci (4 were Staphylococcus aureus), 5 streptococci, 2 Gram-positive bacilli, and 3 mixed growth. Though the mean time to positivity of pathogens grown in both atmospheres was significantly lower in the aerobic bottle than in the anaerobic bottle, in 71 cases (28.4%) the pathogens developed earlier in the anaerobic bottle than in the aerobic bottle – in 36 of these cases at least 1 h earlier, which is significant for starting targeted therapy. *Conclusions:* The use of paired aerobic/anaerobic blood culture bottles allowed the diagnosis of a percentage of bacteraemia due to either anaerobic or aerobic pathogens that would have been missed, as they grew only in the anaerobic atmosphere. Moreover in 8% of bacteraemia we identified a significant decrease in the time to detection, resulting in the opportunity to better manage the infections without an increase in costs.

Keywords: *Bacteraemia, blood culture, growth atmosphere, time-to-positivity, oncological patients*

Introduction

The most valuable test for the laboratory diagnosis of bacteraemia and sepsis is blood culture (BC) [1]: the recovery of pathogens and the timely reporting of identified microorganisms and their antibiotic susceptibility is helpful for the choice of therapy and the appropriate management of infection [2,3]. Usually a routine BC consists of 2 paired aerobic and anaerobic dedicated bottles drawn at the same time from 2 different sites, or, for the diagnosis of central venous catheter (CVC)-related bloodstream infections (BSI), 2 sets from the CVC – the second taken within 1 h – and 1 from a peripheral vein. Depending upon the culture media and the system used, the volume of sample inoculated into each bottle ranges from 8 to 10 ml for adult patients, therefore the sample volume collected in the bottles is about 40 or 60 ml.

Since the 1990s, the decrease in anaerobic BSI reported by some investigators has challenged the need for the routine use of anaerobic bottles, and it has been suggested that the inoculation of the same total volume of sample into 2 aerobic culture bottles is clinically more useful than the use of the aerobic/anaerobic pair, unless anaerobic bacteraemia is suspected [4–11]. However other studies have shown the growth of a number of aerobic microorganisms only in an anaerobic atmosphere, so that the non-use of anaerobic vials exposes the patient to the risk of a missed diagnosis of infection [12–14]. Moreover, the

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overall incidence of anaerobic bacteraemia has recently been reported to be around 8.7% [15]; this is not a negligible percentage, especially considering that the mortality observed in anaerobic bacteraemia is among the highest, ranging from 10% to 55% [16–18].

The purpose of this study was to evaluate the most effective method of detection of bacteraemia in a population of oncology patients, comparing the use of the paired aerobic/anaerobic BC bottles versus the use of only aerobic bottles. We also analyzed the difference in time to growth of pathogens in both atmospheres, aerobic and anaerobic.

Materials and methods

Study design and inclusion criteria

We retrospectively evaluated all consecutive BCs collected from April 2011 to March 2013 at the European Institute of Oncology in Milan, Italy. All patients signed an informed consent form, which allowed the use of their data in future scientific studies. The study population consisted of adult patients admitted to the surgical and medical oncology divisions or to the intensive care unit (ICU) as part of the ordinary or day hospital regime. The patients admitted to the surgical divisions were mainly immunocompetent subjects undergoing treatment for primary and metastatic tumours, while those admitted to the division of medical oncology were predominantly immunosuppressed subjects undergoing chemotherapy for various solid tumours; patients admitted to the division of haematology–oncology were receiving aggressive chemotherapy or high-dose chemotherapy with autologous peripheral blood progenitor cell transplantation or allogeneic stem cell infusions for leukaemia, lymphomas, and solid tumours. During their hospital stay, some patients required a short-term or a long-term CVC for the administration of antibiotics, chemotherapy, or parenteral nutrition.

Data collection

The BCs were collected (1) for the diagnosis of CVC-related BSI (2 sets from the CVC – the second taken within 1 h – and 1 from a peripheral vein at the onset of fever, defined as a single body temperature peak over 38.5°C or a sustained body temperature of more than 38.0°C for 2 observations within 24 h, not being a consequence of the administration of potentially pyrogenic agents), or (2) for the diagnosis and/or the confirmation of a non-catheter-related BSI such as sepsis, pneumonia, or a deep surgical wound infection (2 sets of BCs, both obtained from peripheral venipuncture, if possible, and another set 1 h later). Isolation of coagulase-negative staphylococci (CoNS) or other possible contaminants was considered significant only if detected from multiple cultures or from a clinically compatible event (based both on the clinical situation and other diagnostic investigations and the outcome of therapy).

Laboratory analysis

Twenty millilitres of blood were obtained aseptically and distributed equally into Bactec aerobic/F resin and Bactec Lytic/10 anaerobic/F bottles (Becton Dickinson, Sparks, MD, USA). The bottles were incubated in the Bactec FX Instrument (Becton Dickinson, Sparks, MD, USA) at 35°C, using a 5-day protocol, in accordance with the manufacturer's recommendations. Only bottles that were signalled as positive by the instrument were subcultured. For all positive cultures, the time to positivity, defined as the time from incubation to a positive result, was recorded. An aliquot of the blood–broth mixture from those patients with positive cultures was used for preliminary Gram stain identification and the remaining amount for direct antibiogram following the Kirby–Bauer method (according to the result of the Gram stain). Identification and antimicrobial susceptibility testing were performed using the MicroScan Walk-Away system (Dade Behring SpA) for aerobic Gram-positive and Gram-negative organisms, the Crystal Identification system (Becton Dickinson, Sparks, MD, USA) for anaerobic bacteria, and the API AUX system (bioMérieux) for fungi.

The differential time to positivity (DTP) was used for the diagnosis of CVC-related bacteraemia, defined as an earlier positivity of 120 min or more of central venous versus peripheral BCs [19,20].

Statistical analysis

The numbers of isolates of clinical significance grown in the aerobic and anaerobic bottles were compared using the Fisher' exact test according to the microorganism type. Summary statistics (number, mean, standard deviation, and median) for time to positivity for bacteria (Gram-negative, Gram-positive) and yeasts grown in both aerobic and anaerobic bottles were tabulated. The median time to positivity with 95% confidence intervals (CI) was estimated by Kaplan–Meier method. Comparisons between the mean times for microorganism growth in aerobic and anaerobic bottles were done using the paired *t*-test or the signed rank sum test in the case of non-normality. The departure from normality assumption was tested using the Shapiro–Wilk test. All tests were 2-tailed and considered significant at

the 5% level. All analyses were done using SAS System 9.2 (SAS Institute, Cary, NC, USA).

Results

A total of 2799 BCs were performed for 948 febrile episodes (3 samples/episode collected for the diagnosis of CRBIs and 2 samples/episode for other infections, in agreement with internal European Institute of Oncology guidelines). These episodes occurred in 602 patients, of whom 331 had a long- or short-term CVC; 1330 BCs were drawn from the CVC and 1469 from a peripheral vein. Each blood sample was inoculated in paired aerobic and anaerobic BC bottles, for a total of 5598 bottles. In 487 febrile episodes at least 2 BCs were positive, thus reducing the likelihood of a false-positive due to contamination, with the isolation of 463 aerobes (bacteria or fungi) and 24 anaerobes. Table I shows the comparison of clinically significant isolates grown in the aerobic/anaerobic bottle pairs, by bottle type: 174 isolates (35.7%), all aerobic, grew only in the aerobic bottle; 250 isolates (51.3%), all aerobic, grew in both bottles; and 63 isolates (12.9%) grew only in the anaerobic culture bottle. Of the 63 isolates that grew only in the anaerobic bottle, 24 were anaerobic and 39 were aerobic microorganisms (8% of positive BCs). The pathogens isolated in these 39 cultures were 12 Gram-negative (8.6% of all isolated Gram-negative), 17 staphylococci (8.6% of all isolated staphylococci; 4 were Staphylococcus aureus corresponding to 16% of isolated S. aureus), 5 streptococci (9.6% of isolated streptococci), 2 Gram-positive bacilli, and 3 mixed growth (12% of all mixed growth). Table II provides a summary of the aerobic and anaerobic pathogens grown only in the anaerobic atmosphere.

Table III shows the summary statistics for the time to positivity (TP) of the 250 pathogens grown in both the aerobic and anaerobic bottles. Although the mean TP in the aerobic bottles was significantly shorter than in the anaerobic bottles, in 5.2% of cases (13 samples) the TP was the same, in 66.4% (166 samples) the TP in the aerobic bottle was shorter than in the anaerobic bottle, while in 71 cases (28.4%) the pathogens developed in the anaerobic bottle before the aerobic bottle. In particular, in 36 of these cases the pathogens developed in the

Table I. Comparative yield of 487 clinically significant isolates of bacteria and yeasts from aerobic/anaerobic bottle pairs by bottle type.

Microorganisms	Number of isolates from:			*p*-Value[a]
	Both bottles	Aerobic bottle only	Anaerobic bottle only	
Gram-positive ($n = 252$)	145	83	24	< 0.001
Staphylococcus aureus ($n = 25$)	16	5	4	Not tested
CoNS[b] ($n = 175$)	101	61	13	< 0.001
Enterococci[c] ($n = 33$)	18	13	2	0.007
Streptococcus pneumoniae ($n = 4$)	3	1	0	Not tested
Other streptococci[d] ($n = 13$)	7	3	3	Not tested
Gram-positive bacilli ($n = 2$)	0	0	2	Not tested
Gram-negative ($n = 139$)	87	40	12	< 0.001
Escherichia coli ($n = 46$)	36	4	6	0.754
Pseudomonas species[e] ($n = 18$)	1	17	0	< 0.001
Other Enterobacteriaceae[f] ($n = 69$)	50	13	6	0.167
Other Gram-negative bacilli[g] ($n = 6$)	0	6	0	Not tested
Anaerobes[h] ($n = 24$)	0	0	24	< 0.001
Yeasts[i] ($n = 47$)	4	43	0	< 0.001
Mixed growth of aerobes[l] ($n = 25$)	14	8	3	0.226
Total, *n* (%)	250 (51.3%)	174 (35.7%)	63 (12.9%)	

[a]Aerobic vs anaerobic comparison.
[b]Coagulase-negative staphylococci, including Staphylococcus epidermidis, Staphylococcus auricularis, Staphylococcus capitis, Staphylococcus haemolyticus, Staphylococcus hominis, Staphylococcus simulans, and Staphylococcus warneri isolates.
[c]Includes Enterococcus faecium, Enterococcus faecalis, and Enterococcus avium isolates.
[d]Includes Streptococcus pyogenes, Streptococcus mitis, Streptococcus milleri, Streptococcus bovis, and other Streptococcus isolates.
[e]Includes Pseudomonas aeruginosa and Stenotrophomonas maltophilia isolates.
[f]Includes Enterobacter aerogenes, Enterobacter cloacae, Klebsiella pneumoniae, Klebsiella oxytoca, Serratia marcescens, and other enterobacteria isolates.
[g]Includes Acinetobacter baumannii, Acinetobacter xylosoxidans, and Moraxella species isolates.
[h]Includes Bacteroides thetaiotaomicron, Bacteroides fragilis group, Bacteroides capillosus, Prevotella oralis, Bacteroides uniformis, Propionibacterium avidum, and other anaerobic Gram-negative bacillus isolates.
[i]Includes Candida albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis, and other Candida species isolates.
[l]Includes Gram-positive/Gram-negative, Gram-positive/Gram-positive, Gram-negative/Gram-negative, Gram-negative/yeast, and Gram-positive/yeast isolates.

Table II. Aerobic and anaerobic pathogens grown only in the anaerobic bottles.

Aerobic	
Gram-negative ($n = 12$)	
Escherichia coli	6
Serratia marcescens	1
Klebsiella pneumoniae	3
Enterobacter cloacae	1
Escherichia fergusonii	1
Gram-positive ($n = 24$)	
Coagulase-negative Staphylococcus	13
Staphylococcus aureus	4
Streptococcus species	3
Enterococci	2
Gram-positive bacilli	2
Fungi	0
Mixed growth	3
Aerobic missing/total aerobic	39/463 = 8.4%
Anaerobic	
Gram-negative bacilli	6
Bacillus uniformis	1
Bacteroides fragilis group	5
Prevotella oralis	3
Propionibacterium avidum	1
Bacteroides capillosus	3
Bacteroides thetaiotaomicron	5
Anaerobic missing/total anaerobic	24/24 = 100%
Overall Missing/total growth	63/487 = 12.9%

anaerobic bottles at least 1 h before the aerobic bottle. These 36 microorganisms were Enterobacteriaceae (Escherichia coli and Klebsiella pneumoniae), CoNS, and streptococci (both enterococci and other streptococci).

Discussion

The purpose of treating blood samples using both atmospheres – aerobic and anaerobic – for the microbiological diagnosis of bacteraemia, is to maximize the growth of aerobic, anaerobic, and facultative aerobic/anaerobic microorganisms. The issue of the routine performance of anaerobic BCs has been reported in many articles in the medical literature [16,21,22]. Due to a relative decrease in the number of isolates of obligate anaerobic bacteria and a concomitant increase in the number of isolates of obligate aerobic or facultative anaerobic bacteria and yeasts found in positive BCs over the last 20 y, several authors have called into question the advantage of this choice, suggesting that the use of anaerobic BC vials be limited to those patients with specific diseases or undergoing gynaecological or colorectal surgery procedures [4–11].

However, none of the studies that have supported this view have suggested decreasing the quantity of blood taken following the elimination of the anaerobic BC bottle: the premise is that the entire volume is distributed into 2 aerobic BC bottles to increase the sensitivity of the analysis.

This study showed that the use of the paired aerobic/anaerobic bottles allowed not only the identification of anaerobic species in 4.5% of cases, but also the detection of aerobic bacteria that did not grow in 2 paired aerobic bottles.

As far as anaerobic microorganisms are concerned, our data are in agreement with the percentages of positivity reported in the literature [11,17,23]. However it is important to underline that these BCs were taken from General Surgery, Melanoma and Soft Tissue Sarcoma, and Haemato-Oncology Division patients and not only from patients undergoing colorectal or gynaecological surgery.

Looking at the aerobic bottles, we found a significant difference in the recovery of isolates compared to the anaerobic bottles, with a higher growth of CoNS ($p < 0.001$), enterococci ($p = 0.007$), Pseudomonas species ($p < 0.001$), and yeasts ($p < 0.001$) in the aerobic bottles (Table I). However in 8% of positive BCs, aerobic bacteria developed only under anaerobic conditions, which appears to be in disagreement with the opinion that the use of 2 aerobic bottles would lead to a greater yield than paired aerobic/anaerobic bottles and that the increase in recovery would be due to the increased volume rather than to the anaerobic atmosphere [24].

There could be several reasons for the mismatch between our data and those of other studies, including patient demographics, the system and culture media employed, and the microorganisms isolated. Indeed several authors have reported different recovery of specific species or groups of aerobic microorganisms in an anaerobic atmosphere, and even a different recovery of the same aerobic species depending on the features of the medium employed for anaerobic culture (differences in liquid media formulations and composition, as well as the headspace gas volume between the various vial types). Clearly, each conclusion on the appropriateness of routine anaerobic BC bottle use must be based upon the method and culture medium employed in the laboratory [5].

Lastly, although we did not make a direct comparison between the yield of paired aerobic/anaerobic bottles and 2 aerobic bottles, the growth of some aerobes only in the anaerobic atmosphere occurring by chance can be excluded, as these microorganisms were recovered in 2 or more anaerobic bottles without growth in the aerobic atmosphere.

Another interesting point relates to the comparison of the times to growth of the aerobic microorganisms between the aerobic and anaerobic bottles. The mean TP for bacteria grown both in the aerobic

Table III. Summary statistics for time to positivity (h).

Grown in			*n*	Mean ± SD	Median (95% CI)	*p*-Value
Gram-negative	Aerobic bottle (X)		86	10.0 ± 5.5	10.3 (9.5–10.8)	< 0.001
	Anaerobic bottle (Y)		86	11.6 ± 8.7	10.5 (9.7–11.4)	
	Difference			− 1.6 ± 7.9	− 0.25	
		X > Y	29			
		X = Y	5			
		X < Y	52			
Gram-positive	Aerobic bottle (X)		145	18.4 ± 10.7	16.6 (14.9–18.6)	< 0.001
	Anaerobic bottle (Y)		145	22.1 ± 15.6	17.3 (15.6–19.1)	
	Difference			− 3.6 ± 12.1	− 1.02	
		X > Y	41			
		X = Y	5			
		X < Y	99			
Yeasts	Aerobic bottle (X)		4	5.9 ± 2.7	5.6 (3.5–9.1)	Not tested
	Anaerobic bottle (Y)		4	14.7 ± 11.5	11.8 (4.3–30.7)	
	Difference			− 8.7 ± 12.7	− 3.84	
		X > Y	0			
		X = Y	1			
		X < Y	3			
Mixed growth	Aerobic bottle (X)		15	10.9 ± 4.4	9.4 (7.6–12.9)	< 0.001
	Anaerobic bottle (Y)		15	15.2 ± 6.0	15.0 (9.1–17.7)	
	Difference			− 4.3 ± 4.7	− 2.08	
		X > Y	1			
		X = Y	2			
		X < Y	12			
Overall	Aerobic bottle (X)		250	14.9 ± 9.8	12.7 (11.9–13.7)	< 0.001
	Anaerobic bottle (Y)		250	18.0 ± 13.9	14.3 (13.1–15.4)	
	Difference			− 3.0 ± 10.5	− 0.67	
		X > Y	71			
		X = Y	13			
		X < Y	166			

SD, standard deviation; CI, confidence interval.

atmosphere and in the anaerobic atmosphere was 14.9 and 18.0 h, respectively; however in 36 samples the pathogens developed in the anaerobic bottle at least 1 h before the growth in the aerobic bottle: in these cases the mean TP was 15.25 vs 24.9 h, a lot earlier, and possibly allowing a more timely initiation of targeted treatment.

BSIs, and in particular catheter-related BSIs, represent a significant cause of morbidity and mortality (ranging from 12% to 25%) [25], being a potential limitation in optimizing the dose-intensity of the chemotherapy [26]. Although the prompt initiation of empirical antimicrobial therapy is the cornerstone of the management of patients with a BSI or catheter-related BSI, an accurate and early microbiological diagnosis is essential to guarantee focused timely treatment, crucial to the outcome of patients with chronic diseases such as cancer. Several studies have highlighted that the administration of appropriate antibiotics reduces the mortality rate due to BSI by 30% [27,28]. Unfortunately the microbiological tests have long turnaround times, which often limit their proper clinical use. Although automated techniques for BC have significantly reduced the time to the detection of bacterial growth, one of the main objectives of the microbiology laboratory remains a reduction of this time delay, in order to provide the clinician with timely information regarding targeted therapy as early as possible.

In conclusion, the goal of microbiological investigations is to provide the clinician with all possible data relating to the microorganisms responsible for the blood infection and their susceptibility to antibiotics within a useful time frame. In our experience the use of paired aerobic/anaerobic BC bottles made possible the diagnosis of a percentage of bacteraemia due to anaerobic microorganisms and to aerobic pathogens that grew only in anaerobic bottles that would otherwise have been missed. Moreover in 8% of bacteraemia we found a significant decrease in the time to detection, which could allow a greater opportunity to better manage the infections at an earlier time without an increase in costs.

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