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Title: Comparison of time-to-positivity between two blood culture systems: a detailed analysis down to the genus-level

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Abstract

A recently developed, automated blood culture system and medium improve the time-to-positivity (TTP) for bacteremia. However, there have thus far been no genus-level analyses using this novel system. We evaluated and compared the changes in blood culture TTP between two systems: BacT/Alert 3D with a blood culture medium containing activated charcoal versus the more recent BacT/Alert Virtuo with a blood culture medium containing polymeric beads. This before-and-after study included blood cultures collected between July 2010 and April 2014 (3D, activated charcoal) and between July 2015 and April 2018 (Virtuo, polymeric beads). A total of 554,732 blood cultures were included, 267,935 (48.30%) during the first period and 286,797 (51.70%) during the second period. Overall, 55,611 (10.02%) tested positive for at least one microorganism. The incubation of the blood culture medium in the Virtuo system was associated with reduced TTP for the most prevalent bacteria, those representing 91.72% (n=51,006) of all the positive blood cultures. The median TTP was reduced by 0.99 hours for *Staphylococcus*, *Enterococcus*, *Streptococcus*, *Pseudomonadales*, and most of the genera within the order *Enterobacterales* (except the family *Morganellaceae*). However, strictly anaerobic bacteria belonging to the genus *Bacteroides*, representing 0.85% (n=474) of all positive blood cultures, were detected 4.53 hours later using the Virtuo system. Virtuo was associated with a shorter TTP for most bacteria, but this improvement was heterogeneous to the genus level.

Keywords: Bacteriological Techniques; Bacteremia; Bloodstream Infection; Bacteroides Infection; Time-to-positivity

Introduction

Bloodstream infections (BSI) are frequent and severe systemic infections associated with a 30-day mortality rate of 13–21% [1]. Empiric antimicrobial therapy is usually prescribed but is not always appropriate and should be re-evaluated depending on bacteriological analyses. Thus, fast and accurate pathogen diagnostics lead to better care of patients with BSI [2].

Recent blood culture automated systems have been developed to optimize BSI pathogen detection by improving the broth composition of the blood culture bottles and the monitoring system. The BacT/Alert Virtuo (bioMérieux, Marcy l'Etoile, France; referred to as Virtuo hereafter) automated system presents improved temperature stability and high-fidelity optics compared to the older version BacT/Alert 3D (bioMérieux, Marcy l'Etoile, France; referred to as 3D hereafter) [3]. The Virtuo is intended to be used with a blood culture medium containing antibiotic-binding polymeric beads instead of the former blood culture medium containing activated charcoal [4]. The broth composition of blood cultures with activated charcoal is based on soybean-casein digest with brain heart infusions solids. whereas for blood cultures with polymeric beads the broth composition is based on peptones and yeast extracts without brain heart infusions solids [5]. Polymeric beads provide a cleaner background for Gram-staining and less interference for MALDI-TOF mass spectrometry or molecular assays, compared to activated charcoal.

Time-to-positivity (TTP) of blood cultures is an important parameter to optimize because lower TTP leads to faster pathogen identification, guiding the antimicrobial therapy.

Utilization of the Virtuo with blood culture media containing polymeric beads reduced the time-to-positivity (TTP) of blood cultures for *Enterobacterales* and *Enterococcus* spp., and increased bacterial recovery [3, 4, 6]. However, a detailed genus-level analysis was not feasible in this type of prospective studies because the number of blood culture bottles required would have been prohibitively large. Indeed, only about 10% of the blood culture samples are positive, and most of the bacteria recovered belong to the same genera (*Staphylococcus*, *Escherichia*, *Enterococcus*, or *Streptococcus*) [7]. Thus, the impact of switching to a newer automated system and blood culture medium on the detection of less prevalent bacteria remains unknown.

We performed a large before-and-after study to examine the impact of switching to a modern automated system and blood culture medium. The principal aim was to evaluate the changes in TTP values, detailed to the genus level, between two systems: 3D with a blood culture medium containing activated charcoal versus the more recent Virtuo with a blood culture medium containing polymeric beads.

Methods

This before-and-after study was conducted at Lille University Hospital, a 3,200-bed hospital in France. In the first period from July 2010 to April 2014, BacT/Alert FA (aerobic), FN (anaerobic), or PF (pediatric) blood cultures (containing activated charcoal) were incubated on a 3D automated blood culture system. In the second period from July 2015 to April 2018, BacT/Alert FA Plus (aerobic), FN Plus (anaerobic), or PF Plus (pediatrics) blood cultures (containing polymeric beads) were incubated on a Virtuo. In both periods, bottles were incubated for five days or until they signaled

positive for growth. Blood cultures from May 2014 to June 2015 were excluded from the analysis because they were collected within a transition period during which another blood culture medium (containing polymeric beads) was used on a 3D.

Blood cultures were transferred from the clinical wards to the laboratory using a pneumatic tube system. Positive blood cultures were processed according to standard laboratory protocols. Bacteria were identified using MALDI-TOF mass spectrometry (Bruker Daltonics, Wissembourg, France). If identification at the species level was not possible using MALDI-TOF, 16S rDNA sequencing was performed, as described elsewhere [8].

Data collected included the type of blood culture, time of specimen collection, time of introduction into the automated blood culture system, and time of positivity or negativity. Time-to-positivity was defined as the duration from when the sample was first incubated on the automated blood culture system to signaled positive for growth by the system. The following patient demographic data were automatically collected during the data extraction: age, sex, ward, and date of entry into the hospital. No names or birthdates were included to preserve the privacy of patients, following the recommendations from the French National Commission on Informatics and Liberty.

Polymicrobial blood cultures were not excluded. If a blood culture was positive with multiple species from the same genus (e.g., two different *Staphylococcus* isolates), it was counted only once for this genus. The denominator was the total number of blood culture bottles included and not the number of different bacteria identified.

101 Statistical analyses were performed using R software version 3.6.3 [9]. The statistical
102 unit was blood culture bottles, which were considered individually for the analysis, even
103 if they were sampled as a set. Bacterial names were automatically classified by the
104 AMR R package [10], using the microbial taxonomy from the Catalogue of Life
105 database. Failures or uncertainties in the classification were manually reviewed.
106 Qualitative variables were compared with Fisher's exact test and continuous variables
107 with the Mann–Whitney U test. Survival distributions, as defined by the delay until blood
108 cultures signaled positive for growth, were plotted using the survminer R package.

Results

A total of 554,732 blood cultures were included. Of these, 267,935 (48.30%) were in the charcoal-containing blood culture medium incubated on a 3D, and 286,797 (51.70%) were in the polymeric bead-containing blood culture medium incubated on a Virtuo. In total, 55,611 blood cultures (10.02%) were positive for at least one microorganism, including 1,514 (0.27%) with yeasts. Polymicrobial growth (blood culture positive with multiple microorganisms) was detected in 3,613 (0.65%) blood cultures.

The characteristics of the analyzed blood cultures are provided in Table 1. Samples were collected mainly from patients hospitalized in the medical (35.17%), intensive or critical care (33.88%), surgical (11.08%), emergency (8.73%), and pediatric (5.03%) wards. There were small but statistically significant differences in the following demographic data between the two populations: patients from the Virtuo group were older (58 vs. 60 years), more frequently female (39.03% vs. 40.00%), and more frequently from emergency wards (6.65% vs. 10.66%). The blood culture TTP was lower for the Virtuo (16.53 hours on 3D vs. 15.40 hours on Virtuo, $P<0.0001$). In subgroup analysis, the blood culture TTP was reduced for aerobic blood bottles (15.98 hours on 3D vs. 14.75 hours on Virtuo, $P<0.0001$), for anaerobic blood bottles (17.07 hours vs. 16.65 hours, $P<0.0001$), and for pediatric blood bottles (17.88 hours vs. 15.28 hours, $P<0.0001$).

For Gram-positive bacteria, we compared the most frequent genera, identified in at least 100 blood cultures (Table 2). *Staphylococcus* represented the most prevalent genus, identified in 53.05% of the positive blood cultures, with a lower TTP for the Virtuo.

Enterococcus and *Streptococcus* were present in 6.69% and 5.45% of the positive blood cultures, respectively, also with lower TTP in the second period. The TTP was higher in the Virtuo for *Micrococcus*, which are usually considered contaminating bacteria with little clinical relevance. Table S1 shows the subgroup analysis for Gram-positive bacteria, depending on the type of blood culture bottles.

For Gram-negative bacteria, we compared the most frequent genera, identified in at least 100 blood cultures (Table 3). *Enterobacterales* represented the most frequent order, identified in 28.11% of the positive blood cultures. Of these, the TTP for the Virtuo was lower for genera belonging to the family *Enterobacteriaceae* (*Escherichia*, *Klebsiella*, *Enterobacter*, *Citrobacter*) or *Yersiniaceae* (*Serratia*). However, there were no differences in the detection of two genera belonging to the family *Morganellaceae* (*Proteus* and *Morganella*) despite high numbers of positive blood cultures ($n=556$ and $n=267$, respectively). *Pseudomonas* was identified in 3.20% of the positive blood cultures, and the TTP was lower for the Virtuo. *Bacteroides* were the most frequently strictly anaerobic bacteria identified (0.85% of the positive blood cultures) and had a higher TTP for the Virtuo (26.62 hours on 3D vs. 31.15 on Virtuo, $P<0.0001$). The TTP values of blood cultures positive with *Bacteroides* were plotted as cumulative events in Figure 1. Table S2 shows the subgroup analysis for Gram-negative bacteria, depending on the type of blood culture bottles.

For yeasts, the TTP tended to be lower in the Virtuo, but this was not statistically significant (31.39 vs. 33.50 hours, $P=0.056$).

Discussion

In this before-and-after study on 554,732 blood cultures, incubation with the system combining the Virtuo and polymeric beads was associated with a reduced TTP for the most prevalent bacteria. The median TTP was reduced by 0.99 hours for *Staphylococcus*, *Enterococcus*, *Streptococcus*, *Pseudomonadales*, and most of the genera within the order *Enterobacterales* (except the family *Morganellaceae*), representing 91.72% ($n=51,006$) of all the positive blood cultures.

These results are consistent with previous studies. Altun *et al.* showed that the TTP was significantly reduced in the Virtuo compared with the 3D using simulated blood cultures spiked with 115 bacterial or fungal isolates, for all the bacteria tested (*Enterobacterales*, *Acinetobacter*, *Staphylococcus*, *Enterococcus*, *Streptococcus*) [3]. The TTP was reduced in the Virtuo for both blood culture media, containing either polymeric beads (FA Plus or FN Plus) or activated charcoal (FA or FN). Another study using simulated blood cultures spiked with 330 bacterial or fungal isolates showed a reduction of the TTP in the Virtuo for most microorganisms, except *Stenotrophomonas maltophilia* and some *Candida* species [11]. Additionally, a multicenter study on 5,709 blood culture sets compared the 3D to the Virtuo using either a blood culture medium containing polymeric beads (FA Plus or FN Plus) or a medium containing no beads and no charcoal (SA or SN) [6]. In these conditions, the TTP was reduced by almost 2 hours for the blood cultures incubated on the Virtuo compared to the 3D. The TTP was significantly decreased only for *Enterobacterales* and *Enterococcus*. For *Streptococcus* and coagulase-negative *Staphylococcus*, there was a trend of the Virtuo reducing the TTP, but this effect was not statistically significant ($P=0.08$ and $P=0.10$, respectively). A recent study compared the TTP of the 3D to Virtuo on 1,904 blood culture sets

exclusively using a blood culture medium containing polymeric beads (FA Plus or FN Plus) [12]. The TTP was significantly reduced for *Staphylococcus aureus* (–1.7 hours for the Virtuo) and *Escherichia coli* (–0.6 hours). However, the overall reduction of the TTP for clinically significant pathogens was only 18 minutes, less than the 2-hour reduction reported previously [6]. Finally, another study compared two different periods, one with the 3D, followed by another with the Virtuo, exclusively using a blood culture medium containing polymeric beads (FA Plus, FN Plus, or PF Plus) [13]. The TTP was significantly reduced for *Staphylococcus*, *Enterobacterales*, and *Streptococcus*, while no difference was shown for *Enterococcus*.

In our study, the TTP was reduced in the Virtuo with polymeric beads for *Enterobacterales*, but not for the *Morganellaceae* family. Data on bacteremia due to *Morganellaceae* are scarce [14], even if *Morganellaceae* represented 1.50% of all positive blood cultures in our study. The mechanism by which the *Morganellaceae* TTP is not decreased with the more efficient automated system remains unknown. One hypothesis might reside in activated charcoal inhibiting swarming from *Proteus* [15]. A correlation between swarming and growth rate in liquid medium has been previously suggested [16].

Our results also show that *Bacteroides* was associated with a higher TTP for the Virtuo with polymeric beads compared with the 3D with activated charcoal. In 474 blood culture positive with *Bacteroides*, the median TTP was 4.53 hours higher using the Virtuo ($P < 0.0001$). *Bacteroides* is the most common genus detected in BSI due to strictly anaerobic bacteria. This delayed detection could be clinically relevant. Failure to add appropriate antimicrobials was previously associated with higher mortality (55% vs.

17%) in the case of anaerobic bacteremia (mostly due to *Bacteroides*) [17]. Empirical antimicrobial therapy includes anti-anaerobic coverage for only half of the patients with anaerobic bacteremia [17]. The reasons for this delayed detection remain hypothetical. As the Virtuo improved temperature stability and high-fidelity optics compared to the 3D, the difference in TTP for *Bacteroides* might be linked to the use of a blood culture medium containing polymeric beads. Indeed, De Keukeleire *et al.* compared the performance of two blood culture media containing either polymeric beads (FN plus) or activated charcoal (FN) on the detection of anaerobes with the 3D, using blood cultures experimentally spiked with anaerobic bacteria [18]. The TTP was significantly increased for resin-based compared with charcoal-based blood culture bottles for *Bacteroides* spp. (49 hours vs. 27 hours) and most of the other anaerobes. Rapid diagnosis of bacteremia due to *Bacteroides* would allow for the rapid adaptation of antimicrobial therapy, which may lead to lower mortality.

The principal limitation of our study is the before-and-after design. First, the type of patients included in our hospital may have changed during the study period. Demographic characteristics of the patients were significantly different: in the first period, patients were younger (58 vs. 60 years), more frequently male (60.97% vs. 60.00%), and more frequently hospitalized in intensive or critical care (34.59% vs. 33.22%). All these differences were highly significant ($P < 0.0001$). However, due to a large number of blood cultures included (554,732), even small differences in values could result in statistical significance. Second, additional parameters affecting the TTP of blood cultures include the volume of blood sampled, transportation time, and concomitant antimicrobial therapy, which have not been monitored in our study [19].

222 Finally, different blood culture media and blood culture instruments were compared,
223 resulting in a mixed effect. However, the TTP decrease for the most prevalent bacteria
224 found is consistent with the literature [3, 6, 13] and externally validate our results.

225 Overall, our study confirms the Virtuo and the blood culture medium with polymeric
226 beads are associated with a reduced TTP for the most prevalent bacteria, compared to
227 the 3D system and the blood culture medium with activated charcoal. However, no
228 differences were observed for the family *Morganellaceae*, representing an exception
229 within the order *Enterobacterales*. Moreover, TTP values were even significantly
230 increased for *Bacteroides* using the most modern automated system.

231 **Declarations**

232 **Funding:** This work was supported by CHU Lille.

233 **Competing Interests:** The authors declare that they have no conflict of interest.

234 **Ethical Approval:** The study was approved by the local Institutional Review Board.

235 Patient consent was not requested for this study, since the study was based on
236 anonymized data collected retrospectively.

237 **Consent to Participate:** Formal consents were not required for this retrospective study
238 on anonymized data.

239 **Consent to Publish:** Not applicable.

240 **Availability of data and materials:** All data were anonymized. The dataset analyzed
241 during the current study is available from the corresponding author on reasonable
242 request.

243 **Authors Contributions:** RLG and RD conceived and planned the study. All authors
244 participated in data collection and microbiological analysis. RLG performed the data
245 analysis. RLG and RD wrote the first draft, all authors reviewed and edited the final
246 manuscript.

247

248 **Words:** 2289

249 **Figure Legends**

250 **Figure 1.** Cumulative probability of the time-to-positivity (TTP) for blood cultures
251 positive with *Bacteroides* sp.

252 BacT/Alert 3D = BacT/Alert 3D with the blood culture medium containing activated
253 charcoal; BacT/Alert Virtuo = BacT/Alert Virtuo with the blood culture medium containing
254 polymeric beads.

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311

312 **Table 1.** Characteristics of the included blood culture sample bottles

	BacT/Alert 3D Total (n = 267,935)	BacT/Alert Virtuo Total (n = 286,797)	P-value
Patient demographics characteristics			
Age (years)	58.0 (42.0–70.0)	60.0 (45.0–71.0)	< 0.0001
Sex			< 0.0001
Female	104,554 (39.03%)	114,705 (40.00%)	..
Male	163,355 (60.97%)	172,085 (60.00%)	..
Type of ward			< 0.0001
Medicine	94,750 (35.36%)	100,367 (35.00%)	..
Intensive/critical care	92,676 (34.59%)	95,273 (33.22%)	..
Surgery	30,592 (11.42%)	30,851 (10.76%)	..
Emergency	17,825 (6.65%)	30,583 (10.66%)	..
Pediatric	15,362 (5.73%)	12,530 (4.37%)	..
Geriatric	9,870 (3.69%)	9,511 (3.31%)	..
Rehabilitation	3,740 (1.40%)	4,983 (1.74%)	..
Obstetrics	2,958 (1.10%)	2,576 (0.90%)	..
Psychiatry	162 (0.06%)	123 (0.04%)	..
Blood culture type			< 0.0001
Aerobic	130,598 (48.74%)	141,543 (49.35%)	..
Anaerobic	118,757 (44.32%)	130,893 (45.64%)	..
Pediatric	18,580 (6.94%)	14,361 (5.00%)	..
Positive blood cultures			
Positive blood bottles	25,783 (9.62%)	29,828 (10.40%)	< 0.0001
Time to positivity (hours)	16.53 (11.88–24.63)	15.40 (10.95–22.72)	< 0.0001

313

314 Data are median (IQR) or n (%).

Table 2. Gram-positive bacteria: time-to-positivity (median) and percentage of positivity

Microorganism group			Sample size (n)		Median time to positivity (hours)				Percentage of positivity (%)		
Phylum	Order	Genus	3D	Virtuo	3D	Virtuo	Difference	P-value	3D	Virtuo	P-value
Firmicutes			16,716	19,385							
	Bacillales		13,625	16,123							
		Staphylococcus	13,520	15,984	19.27	18.35	-0.92	< 0.0001	5.05	5.57	< 0.0001
		Bacillus	79	143	12.32	12.9	0.58	0.92	0.03	0.05	< 0.001
	Lactobacillales		3,340	3,512							
		Enterococcus	1,789	1,931	13.05	12.50	-0.55	< 0.001	0.67	0.67	0.81
		Streptococcus	1,506	1,526	13.30	12.46	-0.84	< 0.0001	0.56	0.53	0.13
Actinobacteria			291	386							
	Actinomycetales		262	349							
		Micrococcus	101	145	37.02	43.68	6.66	< 0.001	0.04	0.05	0.03
		Corynebacterium	86	73	47.05	49.58	2.53	0.59	0.03	0.03	0.17

Only genera identified in at least 100 blood cultures are shown. Statistically significant differences in time-to-positivity (TTP) are in bold. 3D = BacT/Alert 3D with the blood culture medium containing activated charcoal; Virtuo = BacT/Alert Virtuo with blood culture medium containing polymeric beads.

Table 3. Gram-negative bacteria: time-to-positivity (median) and percentage of positivity

Microorganism group			Sample size (n)		Median time to positivity (hours)				Percentage of positivity (%)		
Phylum	Order	Genus	3D	Virtuo	3D	Virtuo	Difference	P value	3D	Virtuo	P-value
<i>Proteobacteria</i>			8,248	10,001							
	<i>Enterobacteriales</i>		6,970	8,660							
		<i>Escherichia</i>	3,197	3,791	11.08	10.30	-0.78	< 0.0001	1.19	1.32	< 0.0001
		<i>Klebsiella</i>	1,847	2,367	11.57	10.28	-1.29	< 0.0001	0.69	0.83	< 0.0001
		<i>Enterobacter</i>	1,170	1,581	12.07	10.77	-1.30	< 0.0001	0.44	0.55	< 0.0001
		<i>Serratia</i>	240	319	14.43	12.32	-2.11	< 0.0001	0.09	0.11	0.01
		<i>Proteus</i>	275	281	12.73	13.15	0.42	0.84	0.10	0.10	0.61
		<i>Citrobacter</i>	189	318	11.73	10.76	-0.97	< 0.001	0.07	0.11	< 0.0001
		<i>Morganella</i>	119	148	13.32	12.82	-0.50	0.37	0.04	0.05	0.25
	<i>Pseudomonadales</i>		1,072	1,092							
		<i>Pseudomonas</i>	922	859	17.23	16.35	-0.88	0.03	0.34	0.30	0.004
		<i>Acinetobacter</i>	138	215	13.16	11.80	-1.36	0.04	0.05	0.08	< 0.001
	<i>Xanthomonadales</i>		83	119							
		<i>Stenotrophomonas</i>	83	119	22.58	20.62	-1.96	0.23	0.03	0.04	0.05
<i>Bacteroidetes</i>			298	256							
	<i>Bacteroidales</i>		277	226							
		<i>Bacteroides</i>	261	213	26.62	31.15	4.53	< 0.0001	0.10	0.07	0.004

Only genera identified in at least 100 blood cultures are shown. Statistically significant differences in time-to-positivity (TTP) are in bold. 3D = BacT/Alert 3D with the blood culture medium containing activated charcoal; Virtuo = BacT/Alert Virtuo with the blood culture medium containing polymeric beads.

Figure 1. Cumulative probability of time to positivity for blood cultures positive with *Bacteroides* sp.

BacT/Alert 3D = BacT/Alert 3D with the blood culture medium containing activated charcoal; BacT/Alert Virtuo = BacT/Alert Virtuo with the blood culture medium containing polymeric beads.