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The Impact of Implementing the Virtuo Blood Culture System on the Characteristics and Management of Patients with *Staphylococcus aureus* Bacteremia

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ABSTRACT Persistent *Staphylococcus aureus* bacteremia (SAB) has been associated with increased mortality. Enhanced microbial detection with new blood culture technology may improve detection of *S. aureus* in patients with SAB. We performed a 24-month retrospective study of hospitalized adults with SAB and an infectious diseases consult comparing two time periods pre- (January to December 2018) and postimplementation (January to December 2019) in which the VersaTREK and BacT/Alert Virtuo blood culture systems were used, respectively. Measurements included SAB duration, time to positivity, source of bacteremia, antimicrobial therapy, and mortality. A total of 416 episodes of SAB occurred during the study period: 176 (42%) pre- and 240 (58%) postimplementation. Patients in both periods had similar clinical characteristics; however, patients in the postimplementation period were more likely to have intermediate (3 to 6 days; 23% versus 40%; $P < 0.001$) and prolonged SAB duration (>7 days; 4% versus 14%; $P < 0.001$). Combination antistaphylococcal therapy was more frequent postimplementation (6.3% pre- versus 15.8% postimplementation; $P = 0.003$), and the median time to source control was shorter (4 versus 2 days; $P = 0.02$). Median time to positivity for the index blood culture was shorter postimplementation (17.8 h pre- versus 13.3 h postimplementation; $P < 0.001$). There was no difference in 90-day all-cause readmissions (51% versus 44%; $P = 0.11$) or mortality (32% versus 32%; $P = 0.95$). An increased frequency of prolonged SAB with increased use of combination antistaphylococcal therapy was noted with implementation of a new blood culture system, likely secondary to the blood culture media; however, no differences on adverse outcomes were noted.

KEYWORDS *S. aureus*, bacteremia, blood culture, staphylococcal infections, treatment outcome

Staphylococcus aureus bacteremia (SAB) is a common community- and hospital-onset bloodstream infection (BSI) and is associated with significant morbidity and mortality (1, 2). Delays in diagnosis and appropriate therapy can lead to serious complications, such as endocarditis, osteomyelitis, and death. Several studies have identified persistent bacteremia to be associated with prolonged hospital length of stay, increased risk of embolic complications, and mortality (1, 3). Despite this, randomized trials have failed to find an association between earlier clearance of blood cultures with the use of combination antibiotic therapy and reduced mortality (4). Similarly, the time to blood culture positivity (TTP) has been considered an independent predictor of infective endocarditis and even death (5, 6). While TTP is often thought by clinicians to represent the burden of bacteria and the microbial growth rate in the blood sample, many factors can influence TTP, such as the culture media used, the blood volume collected, and the presence of antibiotics in the blood specimen (7, 8).

Newer blood culture systems have been developed with the goal of providing more rapid detection of microorganisms in the setting of BSI (9). Newer formulations

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of blood culture media, coupled with updated instrumentation algorithms, may allow for faster bacterial growth and inactivation of antibiotics present in the blood, resulting in faster time to detection of microbial growth and possibly higher rate of organism recovery (10). Previous studies have shown that detection rate and TTP can vary among blood cultures systems, especially in the presence of antibiotics (8, 11). The objective of our study was to determine the impact of implementation of the BacT/Alert Virtuo blood culture system (Virtuo; bioMérieux, Durham, NC) on the microbiological characteristics and management of SAB at our institution.

MATERIALS AND METHODS

Setting and study design. We performed a retrospective cohort study of adults hospitalized with SAB at Barnes-Jewish Hospital (BJH), a 1,250-bed academic hospital in St. Louis, Missouri, USA. Starting 14 January 2019, our institution implemented the Virtuo system (bioMérieux, Durham, NC) in replacement of the VersaTREK system (TREK Diagnostic Systems, Cleveland, OH) for analysis of blood cultures.

We divided our cohort into SAB episodes using their initial positive, or index, blood culture in the preimplementation (VersaTREK; 1 January 2018 to 13 January 2019) and postimplementation (Virtuo; 14 January 2019 to 31 December 2019) periods. All episodes of SAB in patients >18 years of age were identified using the BJH medical informatics database. We excluded SAB episodes in patients that died within 48 h after the index blood culture and with recurrent episodes occurring within 90 days of the index blood culture. To standardize the management of SAB throughout the study period, we also excluded patients without an infectious diseases (ID) consult. We did not exclude patients transferred from other hospitals, patients that received antibiotics prior to blood culture collection, or patients with polymicrobial BSI. The study was approved by the Washington University School of Medicine Institutional Review Board with a waiver of informed consent.

Blood culture systems. During the preimplementation period, the VersaTREK system was used with VersaTREK REDOX 1 (aerobic) and REDOX2 (anaerobic) media, which utilized a 1:9 blood/broth dilution to neutralize the effects of antibiotics if present. In the postimplementation period, the Virtuo system was used with FA Plus (aerobic) and FN Plus (anaerobic) media that have polymeric resins that inhibit antibiotics if present in the blood. During both time periods, sampling for suspected bacteremia was standard and included obtaining at least two sets of aerobic and anaerobic bottles from two separate phlebotomy sites. The requested blood volume per blood culture set was 20 mL, divided equally into the aerobic and anaerobic bottles. Obtaining only one set of aerobic and anaerobic bottles in a day or more than one set from a single phlebotomy site or blood sampling from a central line is discouraged. No guidelines exist at our institution regarding the frequency of repeat blood cultures to document clearance, and it is left to the discretion of the clinician. During both time periods, the laboratory loaded blood cultures onto the instrument and processed positive blood cultures 24 h per day, 7 days per week. The incubation period for both systems was up to 5 days or until the blood culture bottle signaled positive for growth. Positive bottles were processed according to laboratory standard operating procedure (12). Final organism identification was made using matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) (Bruker BioTyper, Bruker Daltonics).

Definitions and study outcomes. A SAB episode was defined as a patient having *S. aureus* isolated from at least one blood culture bottle. Determination of methicillin susceptibility of *Staphylococcus aureus* isolates was performed using the Kirby-Bauer disk diffusion method (cefoxitin) in accordance with CLSI standards.

We defined SAB duration as the number of days between the first and last positive blood culture with *S. aureus*. We then divided SAB duration as being short (1 to 2 days), intermediate (3 to 6 days), or prolonged (≥7 days) (3, 13). For the multivariate analyses, we defined persistent bacteremia as ≥3 days of positive blood cultures, based on previous studies that found this duration of bacteremia to be associated with increased mortality (3). Community-onset SAB was defined as the first positive blood culture collected within 48 h of hospital admission; otherwise, it was classified as hospital-onset SAB. TTP was defined as the time from the blood culture bottle being loaded on the instrument until detection as positive by the instrument. We used the shortest TTP if more than one blood culture was positive for *S. aureus* during that day.

The electronic medical records for all SAB episodes were reviewed for demographic variables, ID consultation notes, antibiotic management, echocardiography and imaging studies, and any surgical procedures done for source control, including hardware removal, incision and drainage, etc. Combination antistaphylococcal therapy was defined as use of >1 active antistaphylococcal agent for the treatment of SAB, and not for coverage of a different organism, based upon ID consultation recommendations at any time during treatment. Definitive antibiotic therapy was defined as antibiotic chosen at discharge and/or final antibiotic recommendations by the ID consultant. Final diagnoses, infectious complications, and recommended antibiotic duration were obtained from the ID consultation notes. All-cause 90-day mortality, all-cause 90-day readmission rate, and length of stay in the index hospital stay for the SAB episode were obtained from the medical records.

Statistical analysis. Continuous variables were expressed as medians with interquartile ranges, as appropriate, and assessed using the Mann-Whitney U test. Categorical variables were presented as absolute numbers and frequencies and were compared using chi-square test or Fisher's exact test, as appropriate. We used a two-sided *P* value of <0.05 as a statistically significant result. Variables with a known

increased mortality risk, based on previously published studies, and variables with clinical plausibility were screened for an association with prolonged SAB and all-cause 90-day mortality. A stepwise backwards logistic regression model was performed using variables that had a *P* value of <0.1 on bivariate analysis. Variables were retained in the final model if they had a *P* value of <0.05. Odds ratios (OR) were calculated for the logistic regression model with 95% confidence intervals. We assessed multicollinearity of variables, based on the variance inflation factor, and none were present. Analysis was performed with the use of STATA software version 16.1 (StataCorp, TX, USA).

RESULTS

Study population. A total of 479 SAB episodes were identified in 456 patients during the study period. Twenty-three (5%) were episodes with recurrence of SAB within 90 days of index episode, four (0.8%) patients died within 48 h after index blood culture, and 36 episodes (8% overall; 7.3% pre- versus 8.3% postimplementation; $P = 0.68$) did not have ID consultation. One patient had an episode of SAB >90 days after the index positive blood culture, which was considered a separate episode for purposes of analysis. Thus, a total of 416 episodes in 415 patients were included for analyses: 176 (42%) pre- and 240 (58%) postimplementation. The median age of patients was 58 years, 60% were male, 40% had methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, and 68% were community-onset infections. Clinical characteristics were similar between both periods, except there were more episodes of catheter-related BSI on the preimplementation period ($P = 0.046$) (Table 1).

Blood culture collection and TTP. During both periods, two sets of aerobic and anaerobic bottles were collected for each day of blood culture collection (median 2 sets [interquartile range {IQR} 2 to 2] preimplementation versus 2 sets [IQR 2 to 2] postimplementation; $P = 0.95$), and these were collected on average every 28 h (IQR 23 to 39) in the preimplementation and every 26 h (IQR 23 to 32) in the postimplementation period ($P = 0.058$).

The median TTP for the index blood culture was shorter in the postimplementation period (17.8 [IQR 14 to 23] h pre- versus 13.3 [IQR 10 to 19] h postimplementation, $P < 0.001$), and this difference remained statistically significant up until day 5 of bacteremia. During the postimplementation period, the TTP remained similar on the following days after index blood culture compared to a longer TTP during the first 4 days in the preimplementation period (Fig. 1). A shorter TTP in the index blood culture was a predictor of persistent SAB in the multivariable logistic model (odds ratio [OR] of 0.95 [95% confidence interval {CI} of 0.93 to 0.98]; $P = 0.001$) (Table 2) and remained significant in the postimplementation period using the Virtuo system (supplemental material).

Duration of bacteremia. Episodes had a median duration of SAB of 2 days (range, 1 to 14 days). Postimplementation, episodes had longer median SAB duration (1 [IQR 1 to 3] day pre- versus 3 [IQR 1 to 5] days postimplementation, $P < 0.001$) and were more likely to have intermediate (23% pre- versus 40% postimplementation; $P < 0.001$) and prolonged SAB duration (4% pre- versus 14% postimplementation; $P < 0.001$). By multivariable analysis, the use of Virtuo system during the postimplementation period was associated with persistent SAB (OR 3.2 [95% confidence interval {CI} 1.97 to 5.2]; $P < 0.001$) (Table 2).

SAB management. Echocardiography and imaging studies were ordered equally during both study periods, except for fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) scans, which were obtained more frequently during the postimplementation period (1% pre- versus 5% postimplementation; $P = 0.004$) (Table 1). These studies, with the exception of transthoracic echocardiography, were obtained more frequently among patients with a longer duration of SAB, regardless of study period (short, intermediate, and prolonged SAB; transesophageal echocardiography: 21%, 38%, and 65%, respectively; $P < 0.001$; computed tomography of chest, abdomen, and pelvis: 13%, 21%, 53%, respectively; $P < 0.001$; magnetic resonance imaging of the spine: 12%, 20%, 43%, respectively; $P < 0.001$; FDG-PET/CT: 0%, 3%, 23%, respectively; $P < 0.001$).

The proportion of patients undergoing procedures to achieve source control was similar in both periods ($P = 0.81$), but the median time from index blood culture to

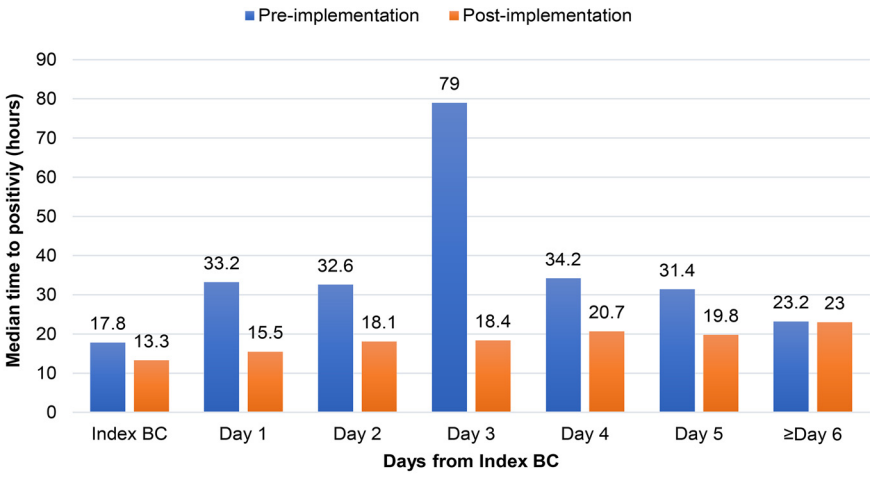
TABLE 1 Clinical characteristics and outcomes of 416 *Staphylococcus aureus* bacteremia episodes by intervention period[a]

Variable, *n* (%) or median (IQR)	Preimplementation[b] (*n* = 176)	Postimplementation[c] (*n* = 240)	*P* value
Age, yrs	57 (46–69)	58 (43–69)	0.92
Sex, male	100 (57)	149 (62)	0.28
Charlson comorbidity index	5 (3–8)	5 (3–8)	0.92
ICU admission within 48 hours after index BC	81 (46)	113 (47)	0.83
ICU admission during hospitalization	97 (55)	134 (56)	0.88
MRSA bacteremia	79 (45)	89 (37)	0.11
Bacteremia onset, community-onset	122 (69)	161 (67)	0.63
Site of infection			
Isolated bacteremia	35 (20)	53 (22)	0.59
Central line-associated bacteremia	50 (28)	48 (20)	0.046
Skin and soft tissue infection	23 (13)	31 (13)	0.96
Osteomyelitis	24 (14)	30 (13)	0.73
Septic arthritis	12 (7)	16 (7)	0.95
Epidural abscess	8 (5)	5 (2)	0.17
Endocarditis	28 (16)	40 (17)	0.84
Vascular graft infection	5 (3)	9 (4)	0.79
Lower respiratory tract infection	18 (10)	28 (12)	0.64
Cardiac device associated infection	10 (6)	10 (4)	0.48
Bacteremia duration, days	1 (1–3)	3 (1–5)	<0.001
Short (1–2 days)	129 (73)	110 (46)	<0.001
Intermediate (3–6 days)	40 (23)	97 (40)	<0.001
Prolonged (>7 days)	7 (4)	33 (14)	<0.001
MSSA, bacteremia duration			
Short (1–2 days)	80 (82)	79 (52)	<0.001
Intermediate (3–6 days)	15 (15)	57 (38)	<0.001
Prolonged (>7 days)	2 (2)	15 (10)	<0.001
MRSA, bacteremia duration			
Short (1–2 days)	49 (62)	31 (35)	0.001
Intermediate (3–6 days)	25 (32)	40 (45)	0.001
Prolonged (>7 days)	5 (6)	18 (20)	0.001
Removable source of infection	109 (62)	149 (63)	0.86
Source removed/controlled	82 (75)	109 (73)	0.74
Time from index BC to source control, days	4 (2–6)	2 (1–6)	0.02
Transthoracic echocardiography	170 (97)	231 (96)	0.85
Transesophageal echocardiography	48 (27)	80 (33)	0.19
Spinal MRI	36 (20)	38 (16)	0.22
CT chest/abdomen/pelvis	27 (15)	53 (22)	0.1
FDG-PET/CT	1 (1)	13 (5)	0.005
Outcomes			
Hospital length of stay, days	16 (8–28)	17 (9–31)	0.29
90-day all-cause readmission	91 (52)	105 (44)	0.11
90-day all-cause mortality	57 (32)	77 (32)	0.95

[a]IQR, interquartile range; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; BC, blood culture; MRI, magnetic resonance imaging; CT, computed tomography; FDG-PET/CT, fluorodeoxyglucose-positron emission tomography/computed tomography.
[b]Preimplementation period from 1 January 2018 to 13 January 2019.
[c]Postimplementation period from 14 January 2019 to 31 December 2019.

source control was shorter in the postimplementation period (4 [IQR 2 to 6] days pre- versus 2 [1 to 6] days postimplementation; $P = 0.02$) (Table 1). A longer time to source control was observed based on duration of bacteremia, regardless of study period (short, intermediate, and prolonged: 2, 4, 10 days, respectively, $P = 0.004$).

Vancomycin was the most common antibiotic used as initial and definitive therapy during both periods but was used less frequently as definitive therapy in the postimplementation period. None of the antibiotics used as initial therapy were associated with persistent SAB in the multivariate analysis (Table 2). Linezolid, ceftaroline,



	Index BC	Day 1	Day 2	Day 3	Day 4	Day 5	≥Day 6
p value*	<0.001	<0.001	<0.001	<0.001	<0.001	0.01	0.42
Pre-implementation†, n (%)	176 (100)	55 (31.3)	38 (21.6)	9 (5.1)	10 (5.7)	7 (4)	7 (4)
Post-implementation‡, n (%)	240 (100)	133 (55.4)	105 (43.8)	80 (33.3)	49 (20.4)	40 (16.7)	33 (13.8)

FIG 1 Median time to positivity (hours) by day of blood culture, by study period. *, Compares median time to positivity between pre- and postimplementation periods in any given day. †, Preimplementation period from 1 January 2018 to 13 January 2019. ‡, Postimplementation period from 14 January 2019 to 31 December 2019. BC, blood culture.

cefazolin, and antistaphylococcal penicillins were used significantly more often in the postimplementation period as definitive therapy (Table 3). Combination antistaphylococcal therapy was used more frequently in the postimplementation period (6% pre- versus 16% postimplementation; $P = 0.003$), with daptomycin plus ceftaroline being the most frequent combination therapy (Table 3). Patients with longer durations of SAB were more likely to have received combination antistaphylococcal therapy, across both study periods (short, intermediate, and prolonged; 3%, 14%, and 58%, respectively; $P < 0.001$). The median planned duration of intravenous antibiotics did not vary between pre- and postimplementation periods (6 [4 to 6] weeks pre- versus 6 [4 to 6] weeks postimplementation, $P = 0.32$).

Clinical outcomes. The median hospital length of stay (16 [IQR 8 to 28] days pre- versus 17 [9 to 31] days postimplementation; $P = 0.29$), 90-day all-cause readmissions (52% pre- versus 44% postimplementation; $P = 0.11$), and 90-day all-cause mortality (32% pre- versus 32% postimplementation; $P = 0.95$) did not differ between study periods. These outcomes were not significantly different by duration of bacteremia in either study period.

Predictors of mortality. Age, lower respiratory tract infection, and linezolid use were predictors of increased all-cause 90-day mortality, while osteomyelitis had decreased risk of 90-day mortality in the final prediction model (Table 4), showing an acceptable goodness-of-fit measured by the Hosmer-Lemeshow test (χ^2-statistic = 7.18, $P = 0.52$).

DISCUSSION

Blood cultures are an important aspect of SAB diagnosis and management, with clearance of bacteremia being one of the immediate goals of therapy. In our study, after our laboratory implemented the Virtuo system, we observed an increased frequency of persistent SAB (≥3 days) and shorter TTP of blood cultures compared to those observed with the previous blood culture system. SAB episodes in the postimplementation period were associated with an increased use of FDG-PET/CT scans and combination antistaphylococcal therapy, plus a shorter time to source control, without a significant change in mortality or readmissions compared to those of SAB episodes in the preimplementation period.

TABLE 2 Bivariate and multivariate analyses of factors associated with persistent bacteremia among 416 *Staphylococcus aureus* bacteremia episodes[a]

Variable, *n* (%) or median (IQR)	Short bacteremia (*n* = 239)	Intermediate-prolonged bacteremia (*n* = 177)	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
Age, yrs	57 (43–68)	59 (44–70)	1.01 (0.99–1.02)	
Sex, male	145 (61)	104 (59)	0.92 (0.62–1.37)	
Charlson comorbidity index	5 (3–8)	5 (3–8)	1.02 (0.96–1.09)	
ICU admission within 48 hours of index BC	109 (46)	85 (48)	1.11 (0.75–1.63)	
ICU admission during hospitalization	128 (54)	103 (58)	1.21 (0.82–1.79)	
MRSA bacteremia	80 (33)	88 (50)	1.97 (1.32–2.93)	2.66 (1.68–4.21)
Bacteremia onset, community-onset	146 (61)	137 (77)	2.18 (1.41–3.38)	1.7 (1.04–2.77)
Postimplementation period	110 (46)	130 (74)	3.24 (2.13–4.93)	3.2 (1.97–5.2)
Site of infection				
Isolated bacteremia	58 (24)	30 (17)	0.64 (0.39–1.04)	
Central line-associated bacteremia	69 (29)	29 (16)	0.48 (0.30–0.79)	
Skin and soft tissue infection	30 (13)	24 (14)	1.09 (0.61–1.94)	
Osteomyelitis	22 (9)	32 (18)	2.17 (1.22–3.9)	
Septic arthritis	11 (5)	17 (10)	2.2 (1.0–4.83)	2.73 (1.1–6.77)
Epidural abscess	4 (2)	9 (5)	3.15 (0.95–10.4)	4.47 (1.19–16.8)
Endocarditis	25 (10)	43 (24)	2.75 (1.6–4.7)	2.82 (1.51–5.26)
Vascular graft infection	6 (3)	8 (5)	1.84 (0.63–5.4)	
Lower respiratory tract infection	29 (12)	17 (10)	0.77 (0.41–1.45)	
Cardiac device associated infection	12 (5)	8 (5)	0.9 (0.36–2.24)	
Time to positivity of index BC, h	19 (15–24)	14.7 (12–19)	0.94 (0.92–0.97)	0.95 (0.93–0.98)
Source removed/controlled	113 (47)	78 (44)	0.88 (0.59–1.3)	
Time from index BC to source control, days[c]	2 (1–5)	4 (1–10)	1.08 (1.02–1.14)	
Initial antistaphylococcal therapy				
Vancomycin	188 (79)	142 (80)	1.1 (0.7–1.78)	
Daptomycin	3 (1)	4 (2)	1.82 (0.4–8.2)	
Linezolid	14 (6)	7 (4)	0.66 (0.26–1.68)	
Cefazolin	6 (3)	3 (2)	0.67 (0.17–2.71)	
Antistaphylococcal penicillin	4 (2)	4 (2)	1.36 (0.34–5.51)	

[a]IQR, interquartile range; OR, odds ratio; CI, confidence intervals; BC, blood culture; ICU, intensive care unit; MRSA, methicillin-resistant *S. aureus*.
[b]Variables included in the final logistic regression model were MRSA bacteremia, bacteremia onset, postimplementation period, isolated bacteremia, central line-associated bacteremia, osteomyelitis, septic arthritis, epidural abscess, endocarditis, and time to positivity of index BC.
[c]Time from index BC to source control included 191 *Staphylococcus aureus* bacteremia episodes and was analyzed in a different logistic regression model (supplemental material).

Previous studies have shown detection rates of *S. aureus* with the Virtuo system similar to those with other blood culture systems (11, 14–20). However, in the presence of antibiotics, other commercially available blood cultures systems showed better recovery rate than the VersaTREK system (21, 22). Our group has previously reported that the blood cultures performed on the Virtuo system had a positivity rate for *S. aureus* recovery overall higher than that of the VersaTREK system (1.5% pre- versus 3.4% postimplementation, $P < 0.001$) during the same study period (10). Interestingly, we found that the use of Virtuo system in the postimplementation period was independently associated with a longer duration of bacteremia, despite patients having similar clinical characteristics and outcomes, and similar frequency and number of blood culture bottles collected. To our knowledge, this is the first study to demonstrate that a new blood culture system may increase observed SAB duration and, thus, possibly influence SAB management due to the perception of failing to clear blood cultures. In previous studies, resin-based media showed an advantage in inhibition of antibiotics (23), and it is possible that the resins present in the FA Plus and FN Plus media of the Virtuo system inhibited antibiotic activity in the blood samples better than the REDOX 1 and 2 media from the VersaTREK system, increasing recovery of *S. aureus* from blood specimens despite patients being on appropriate antibiotic therapy. Thus, we believe that the media composition, rather than the instrument itself, was the principal factor affecting recovery of *S. aureus* in the subsequent repeat blood cultures, causing an increase of the overall positivity rate and longer observed duration of SAB. However, we cannot rule

TABLE 3 Antibiotic therapy of 416 *Staphylococcus aureus* bacteremia episodes, by study period

Variable, *n* (%)	Preimplementation (*n* = 176)[a]	Postimplementation (*n* = 240)[b]	*P* value
Initial antistaphylococcal therapy[c]			
Vancomycin	133 (76)	197 (82)	0.11
Daptomycin	5 (3)	2 (1)	0.12
Linezolid	8 (5)	13 (5)	0.69
Ceftaroline	2 (1)	4 (2)	0.65
Cefazolin	2 (1)	7 (3)	0.31
Ceftriaxone	11 (6)	14 (6)	0.86
Antistaphylococcal penicillin	2 (1)	6 (3)	0.48
No antibiotics	0 (0)	2 (1)	0.34
Definitive antibiotic therapy[d]			
Vancomycin	61 (35)	52 (22)	0.003
Daptomycin	19 (11)	36 (15)	0.21
Linezolid	2 (1)	11 (5)	0.05
Ceftaroline	11 (6)	33 (14)	0.01
Cefazolin	27 (14)	58 (24)	0.027
Ceftriaxone	41 (23)	38 (16)	0.055
Antistaphylococcal penicillin	21 (12)	47 (20)	0.037
Combination antistaphylococcal therapy	11 (6)	38 (16)	0.003
Daptomycin-ceftaroline	6 (3)	23 (10)	0.02
Vancomycin-ceftaroline	2 (1)	5 (2)	0.7
Vancomycin-β-lactams	2 (1)	10 (4)	0.08
Other combinations	1 (1)	0 (0)	0.23
Recommended treatment duration, wks, median (IQR)	6 (4–6)	6 (4–6)	0.32

[a]Preimplementation period from 1 January 2018 to 13 January 2019.
[b]Postimplementation period from 14 January 2019 to 31 December 2019.
[c]Antibiotic therapy within the day of index blood culture.
[d]Antibiotic therapy at discharge or final infectious diseases recommendations.

out that instrument detection algorithms and constant incubation temperature were also contributing factors.

We also observed a faster TTP with the new blood culture system, and this was almost unchanged on the following repeat positive blood cultures, despite antibiotic therapy. Previously, other studies have observed a decreased TTP using Virtuo compared to that using other blood culture systems using simulated samples inoculated with different concentrations of microorganisms (11, 14, 15, 17, 18, 24), including that using VersaTREK system (8). In our cohort, neither SAB duration nor TTP in the index blood culture was associated with mortality at 90 days. Other studies have found TTP to be associated with increased mortality (6, 25); however, they used blood culture systems (Bactec FX [Becton, Dickinson; BD] and Bactec 9240 [BD]/BacT/Alert [bioMérieux], respectively) different from those used in our study. Our findings suggest that the observed duration of SAB and faster TTP represented characteristics of the blood culture systems and not necessarily the severity of the SAB. Further studies should take into consideration the blood culture system being used when assessing duration of bacteremia and TTP positivity as clinical predictors of SAB outcomes.

Clinical guidelines recommend that persistent bacteremia of 7 days should prompt an assessment to change therapy if indicated (26), based on older studies in which a median time of 7 days of bacteremia was expected for clearance in patients with MRSA and infective endocarditis (27). More recently, a study reported that each additional day of bacteremia was associated with adverse outcomes, including mortality, and suggested changes in management if bacteremia persisted for 3 or more days (3). None of these studies, however, specified what blood culture system or media they used. We found that implementation of a new blood culture system affected the duration of

TABLE 4 Predictors for 90-day mortality from initial positive blood culture among 416 *Staphylococcus aureus* bacteremia episodes[a]

Variable, *n* (%) or median (IQR)	Survived (*n* = 282)	Died (*n*= 134)	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
Age, yrs	56 (39–67)	62.5 (51–71)	1.03 (1.01–1.04)	1.03 (1.02–1.05)
Sex, male	173 (61)	76 (57)	0.83 (0.54–1.25)	
Charlson comorbidity index	5 (3–8)	6 (3–8)	1.02 (0.96–1.09)	
ICU admission within 48 h of index BC	131 (46)	63 (47)	1.02 (0.68–1.54)	
ICU admission during hospitalization	158 (56)	73 (54)	0.94 (0.62–1.42)	
MRSA bacteremia	114 (40)	54 (40)	0.99 (0.65–1.51)	
Bacteremia onset, community-onset	196 (70)	87 (65)	0.81 (0.53–1.26)	
Postimplementation period	163 (58)	77 (57)	0.98 (0.65–1.5)	
Site of infection				
Isolated bacteremia	59 (21)	29 (22)	1.04 (0.63–1.72)	
Central line-associated bacteremia	61 (22)	37 (28)	1.38 (0.86–2.22)	
Skin and soft tissue infection	34 (12)	20 (15)	1.28 (0.71–2.32)	
Osteomyelitis	43 (15)	11 (8)	0.5 (0.25–1)	0.43 (0.21–0.89)
Septic arthritis	23 (8)	5 (4)	0.44 (0.16–1.17)	
Epidural abscess	10 (4)	3 (2)	0.62 (0.17–2.3)	
Endocarditis	45 (16)	23 (17)	1.09 (0.63–1.89)	
Vascular graft infection	7 (2)	7 (5)	2.17 (0.74–6.3)	
Lower respiratory tract infection	23 (8)	23 (17)	2.33 (1.26–4.33)	2.2 (1.13–4.11)
Cardiac device associated infection	14 (5)	6 (4)	0.9 (0.34–2.39)	
Bacteremia duration, intermediate/prolonged (≥3 days)	116 (41)	61 (46)	1.2 (0.79–1.81)	
Time to positivity of index BC, hours	16 (12–21)	14 (11–20)	1 (0.99–1.02)	
Source removed/controlled	141 (50)	50 (37)	0.6 (0.39–0.91)	
Time from index BC to source control, days	3 (1–6)	3.5 (1–6)	1.02 (0.97–1.07)	
Initial antistaphylococcal therapy				
Vancomycin	230 (82)	100 (75)	0.66 (0.41–1.09)	
Daptomycin	6 (2)	1 (1)	0.35 (0.04–2.9)	
Linezolid	11 (4)	10 (7)	1.99 (0.82–4.8)	
Cefazolin	6 (2)	3 (2)	1.05 (0.26–4.3)	
Antistaphylococcal penicillin	6 (2)	2 (1)	0.7 (0.14–3.5)	
Definitive antistaphylococcal therapy				
Vancomycin	74 (26)	39 (29)	1.15 (0.73–1.82)	
Daptomycin	39 (14)	16 (12)	0.84 (0.45–1.57)	
Linezolid	5 (2)	8 (6)	3.52 (1.13–10.97)	3.79 (1.15–12.51)
Cefazolin	58 (21)	27 (20)	0.97 (0.58–1.63)	
Antistaphylococcal penicillin	50 (18)	18 (13)	0.72 (0.4–1.29)	
Ceftriaxone	54 (19)	25 (19)	0.97 (0.57–1.64)	
Combination antistaphylococcal therapy	29 (10)	20 (15)	1.53 (0.83–2.82)	

[a]IQR, interquartile range; OR, odds ratio; CI, confidence intervals; BC, blood culture; ICU, intensive care unit; MRSA, methicillin-resistant *S. aureus*.
[b]Variables included for consideration in the logistic regression model were age, osteomyelitis, lower respiratory tract infection, source removed/controlled, and linezolid use as definitive antistaphylococcal therapy.

bacteremia without changes in clinical outcomes but did affect management of SAB. Combination therapy in SAB is still controversial, with studies showing time to clearance of blood cultures shorter than that of monotherapy but no significant mortality benefit (4, 28). It is possible that these studies may have influenced our ID physicians' practice, causing increased use of combination therapy during the postimplementation period; however, the observed shorter time to source control and the increased ordering of FDG-PET/CT scans suggest a more aggressive overall approach with the longer observed duration of bacteremia during the postimplementation period. Similarly, although a longer time to source control has been associated with prolonged bacteremia (3), in our study the overall time to source control was shorter in the postimplementation period. This may be due to the longer observed SAB duration, increasing the perceived need for source control by the treating physicians.

Our study has some limitations. First, this is a single-center, retrospective study, and it may not be representative of other hospitals. However, our 90-day mortality was similar to that of a previous study (29), and the 30-day mortality (15%) was also similar to that of other studies (30, 31). Second, our institution previously used the VersaTREK

system, which may not be used at other institutions, and implementation of a new blood culture system may not have the same effect as that seen in our cohort. However, our study raises the important consideration of increased detection of organisms on subsequent blood cultures when implementing newer blood culture systems and the possibility of this affecting patient management. Third, we could not account for all potential factors affecting performance of a blood culture system, such as blood volume for each blood culture bottle collected, transport time to the laboratory, number of participants with polymicrobial bacteremia or those that had blood culture obtained from a central line catheter, or the timing/level of antibiotic prior to blood culture collection. Yet, we accounted for the number and frequency of blood culture bottles collected, and we did not observe an increase in blood volume per bottle during the postimplementation period in the small, random subset of bottles analyzed as part of laboratory quality assurance (data not shown). Fourth, we cannot account for other potential temporal factors that may have influenced SAB management in the postimplementation period, such as newer publications of combination therapy and usefulness of imaging modalities; however, no new SAB clinical guidelines have been published since 2011, and no changes in institution guidelines or blood culture collection practices were instituted between both periods in our study. Finally, due to the observational design, we cannot account for unmeasured confounding factors that may have influenced our final mortality prediction model.

Conclusion. We found that implementation of a new blood culture system was associated with an observed increase in prolonged SAB, likely from the blood culture media, and changes in the ID physicians' clinical approach toward SAB but was not associated with worsening clinical outcomes. ID physicians and future clinical guidelines should consider the blood culture system used at their institution when assessing bacteremia duration and TTP in their decision-making process for the treatment of SAB.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

REFERENCES

1. van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB. 2012. Predictors of mortality in Staphylococcus aureus bacteremia. Clin Microbiol Rev 25:362–386. https://doi.org/10.1128/CMR.05022-11.
2. Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG, Jr. 2015. Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev 28:603–661. https://doi.org/10.1128/CMR.00134-14.
3. Minejima E, Mai N, Bui N, Mert M, Mack WJ, She RC, Nieberg P, Spellberg B, Wong-Beringer A. 2020. Defining the breakpoint duration of Staphylococcus aureus bacteremia predictive of poor outcomes. Clin Infect Dis 70:566–573. https://doi.org/10.1093/cid/ciz257.
4. Tong SYC, Lye DC, Yahav D, Sud A, Robinson JO, Nelson J, Archuleta S, Roberts MA, Cass A, Paterson DL, Foo H, Paul M, Guy SD, Tramontana AR, Walls GB, McBride S, Bak N, Ghosh N, Rogers BA, Ralph AP, Davies J, Ferguson PE, Dotel R, McKew GL, Gray TJ, Holmes NE, Smith S, Warner MS, Kalimuddin S, Young BE, Runnegar N, Andresen DN, Anagnostou NA, Johnson SA, Chatfield MD, Cheng AC, Fowler VG, Howden BP, Meagher N, Price DJ, van Hal SJ, O'Sullivan MVN, Davis JS, Australasian Society for Infectious Diseases Clinical Research Network. 2020. Effect of vancomycin or daptomycin with vs without an antistaphylococcal β-lactam on mortality, bacteremia, relapse, or treatment failure in patients with MRSA bacteremia: a randomized clinical trial. JAMA 323:527–537. https://doi.org/10.1001/jama.2020.0103.
5. Siméon S, Le Moing V, Tubiana S, Duval X, Fournier D, Lavigne J-P, Erpelding M-L, Gustave C-A, Desage S, Chirouze C, Vandenesch F, Tattevin P, Chirouze C, Curlier E, Descottes-Genon C, Hoen B, Patry I, Vettoretti L, Chavanet P, Eicher J-C, Gohier-Treuvelot S, Greusard M-C, Neuwirth C, Péchinot A, Piroth L, Célard M, Cornu C, Delahaye F, Hadid M, Rausch P, Coma A, Galtier F, Géraud P, Jean-Pierre H, Le Moing V, Sportouch C, Reynes J, Aissa N, Doco-Lecompte T, Goehringer F, Keil N, Letranchant L, Malela H, May T, Selton-Suty C, Bedos N, Lavigne J-P, Lechiche C, Sotto A, Duval X, et al. 2019. Time to blood culture positivity: an independent predictor of infective endocarditis and mortality in patients with Staphylococcus aureus bacteraemia. Clin Microbiol Infect 25:481–488. https://doi.org/10.1016/j.cmi.2018.07.015.
6. Kahn F, Resman F, Bergmark S, Filiptsev P, Nilson B, Gilje P, Rasmussen M. 2020. Time to blood culture positivity in Staphylococcus aureus bacteremia is useful to determine the risk for infective endocarditis. Clin Microbiol Infect 27:1345.e7–1345.e12. https://doi.org/10.1016/j.cmi.2020.11.007.
7. Lamy B. 2019. Blood culture time-to-positivity: making use of the hidden information. Clin Microbiol Infect 25:268–271. https://doi.org/10.1016/j.cmi.2018.12.001.
8. Yarbrough ML, Wallace MA, Burnham CD. 2021. Comparison of microorganism detection and time to positivity in pediatric and standard media from three major commercial continuously monitored blood culture systems. J Clin Microbiol 59:e0042921. https://doi.org/10.1128/JCM.00429-21.
9. Lamy B, Sundqvist M, Idelevich EA, ESCMID Study Group for Bloodstream Infections, Endocarditis and Sepsis (ESGBIES). 2020. Bloodstream infections - standard and progress in pathogen diagnostics. Clin Microbiol Infect 26:142–150. https://doi.org/10.1016/j.cmi.2019.11.017.
10. Chavez MA, Munigala S, Burnham CD, Yarbrough ML, Warren DK. 2021. Real-world evaluation of the impact of implementation of the virtuo blood culture system in a tertiary care hospital. J Clin Microbiol 59:e0061721. https://doi.org/10.1128/JCM.00617-21.
11. Totty H, Ullery M, Spontak J, Viray J, Adamik M, Katzin B, Dunne WM, Deol P. 2017. A controlled comparison of the BacT/ALERT 3D and VIRTUO^{TM} microbial detection systems. Eur J Clin Microbiol Infect Dis 36:1795–1800. https://doi.org/10.1007/s10096-017-2994-8.
12. Ransom EM, Alipour Z, Wallace MA, Burnham CA. 2021. Evaluation of optimal blood culture incubation time to maximize clinically relevant results

from a contemporary blood culture instrument and media system. J Clin Microbiol 59 https://doi.org/10.1128/JCM.02459-20.
13. Hawkins C, Huang J, Jin N, Noskin GA, Zembower TR, Bolon M. 2007. Persistent Staphylococcus aureus bacteremia: an analysis of risk factors and outcomes. Arch Intern Med 167:1861–1867. https://doi.org/10.1001/archinte.167.17.1861.
14. Menchinelli G, Liotti FM, Fiori B, De Angelis G, D'Inzeo T, Giordano L, Posteraro B, Sabbatucci M, Sanguinetti M, Spanu T. 2019. In vitro evaluation of BACT/ALERT(R) VIRTUO(R), BACT/ALERT 3D(R), and BACTEC FX automated blood culture systems for detection of microbial pathogens using simulated human blood samples. Front Microbiol 10:221. [PMC] . https://doi.org/10.3389/fmicb.2019.00221.
15. Kim SC, Lee S, Kim S, Cho OH, Park H, Yu SM. 2019. Comparison of clinical performance between BacT/Alert Virtuo and BacT/Alert 3D blood culture systems. Ann Lab Med 39:278–283. https://doi.org/10.3343/alm.2019.39.3.278.
16. Jacobs MR, Mazzulli T, Hazen KC, Good CE, Abdelhamed AM, Lo P, Shum B, Roman KP, Robinson DC. 2017. Multicenter clinical evaluation of BacT/Alert Virtuo blood culture system. J Clin Microbiol 55:2413–2421. https://doi.org/10.1128/JCM.00307-17.
17. Altun O, Almuhayawi M, Lüthje P, Taha R, Ullberg M, Özenci V. 2016. Controlled evaluation of the new BacT/Alert Virtuo blood culture system for detection and time to detection of bacteria and yeasts. J Clin Microbiol 54:1148–1151. https://doi.org/10.1128/JCM.03362-15.
18. Somily AM, Habib HA, Torchyan AA, Sayyed SB, Absar M, Al-Aqeel R, Binkhamis AK. 2018. Time-to-detection of bacteria and yeast with the BACTEC FX versus BacT/Alert Virtuo blood culture systems. Ann Saudi Med 38:194–199. https://doi.org/10.5144/0256-4947.2018.194.
19. Park J, Han S, Shin S. 2017. Comparison of growth performance of the BacT/ALERT VIRTUO and BACTEC FX blood culture systems under simulated bloodstream infection conditions. Clin Lab 63:39–46. https://doi.org/10.7754/Clin.Lab.2016.160502.
20. Congestrì F, Pedna MF, Fantini M, Samuelli M, Schiavone P, Torri A, Bertini S, Sambri V. 2017. Comparison of 'time to detection' values between BacT/ALERT VIRTUO and BacT/ALERT 3D instruments for clinical blood culture samples. Int J Infect Dis 62:1–5. https://doi.org/10.1016/j.ijid.2017.06.012.
21. Li G, Sun J, Pan S, Li W, Zhang S, Wang Y, Sun X, Xu H, Ming L. 2019. Comparison of the performance of three blood culture systems in a Chinese tertiary-care hospital. Front Cell Infect Microbiol 9:285. https://doi.org/10.3389/fcimb.2019.00285.
22. Miller NS, Rogan D, Orr BL, Whitney D. 2011. Comparison of BD Bactec Plus blood culture media to VersaTREK Redox blood culture media for detection of bacterial pathogens in simulated adult blood cultures containing therapeutic concentrations of antibiotics. J Clin Microbiol 49:1624–1627. https://doi.org/10.1128/JCM.01958-10.
23. Lovern D, Katzin B, Johnson K, Broadwell D, Miller E, Gates A, Deol P, Doing K, van Belkum A, Marshall C, Mathias E, Dunne WM. 2016. Antimicrobial binding and growth kinetics in BacT/ALERT FA Plus and BACTEC Aerobic/F Plus blood culture media. Eur J Clin Microbiol Infect Dis 35:2033–2036. https://doi.org/10.1007/s10096-016-2759-9.
24. Chung Y, Kim I-H, Han M, Kim HS, Kim H-S, Song W, Kim J-S. 2019. A comparative evaluation of BACT/ALERT FA PLUS and FN PLUS blood culture bottles and BD BACTEC Plus aerobic and anaerobic blood culture bottles for antimicrobial neutralization. Eur J Clin Microbiol Infect Dis 38:2229–2233. https://doi.org/10.1007/s10096-019-03663-3.
25. Khatib R, Riederer K, Saeed S, Johnson LB, Fakih MG, Sharma M, Tabriz MS, Khosrovaneh A. 2005. Time to positivity in Staphylococcus aureus bacteremia: possible correlation with the source and outcome of infection. Clin Infect Dis 41:594–598. https://doi.org/10.1086/432472.
26. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, Kaplan SL, Karchmer AW, Levine DP, Murray BE, J Rybak M, Talan DA, Chambers HF, Infectious Diseases Society of America. 2011. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis 52:e18-55. https://doi.org/10.1093/cid/ciq146.
27. Levine DP, Fromm BS, Reddy BR. 1991. Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant Staphylococcus aureus endocarditis. Ann Intern Med 115:674–680. https://doi.org/10.7326/0003-4819-115-9-674.
28. Kale-Pradhan PB, Giuliano C, Jongekrijg A, Rybak MJ. 2020. Combination of vancomycin or daptomycin and beta-lactam antibiotics: a meta-analysis. Pharmacotherapy 40:648–658. https://doi.org/10.1002/phar.2437.
29. Hanses F, Spaeth C, Ehrenstein BP, Linde HJ, Schölmerich J, Salzberger B. 2010. Risk factors associated with long-term prognosis of patients with Staphylococcus aureus bacteremia. Infection 38:465–470. https://doi.org/10.1007/s15010-010-0059-3.
30. Turnidge JD, Kotsanas D, Munckhof W, Roberts S, Bennett CM, Nimmo GR, Coombs GW, Murray RJ, Howden B, Johnson PDR, Dowling K, Australia New Zealand Cooperative on Outcomes in Staphylococcal Sepsis. 2009. Staphylococcus aureus bacteraemia: a major cause of mortality in Australia and New Zealand. Med J Aust 191:368–373. https://doi.org/10.5694/j.1326-5377.2009.tb02841.x.
31. Benfield T, Espersen F, Frimodt-Møller N, Jensen AG, Larsen AR, Pallesen LV, Skov R, Westh H, Skinhøj P. 2007. Increasing incidence but decreasing in-hospital mortality of adult Staphylococcus aureus bacteraemia between 1981 and 2000. Clin Microbiol Infect 13:257–263. https://doi.org/10.1111/j.1469-0691.2006.01589.x.