Antibiotic utilization improvement with the Nanosphere Verigene Gram-Positive Blood Culture assay

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New technologies offer rapid identification of organisms and antimicrobial resistance markers in blood cultures several hours faster than conventional methods. We sought to determine whether implementation of the Verigene® Gram-Positive Blood Culture (BC-GP) assay paired with a well-defined results reporting algorithm would lead to earlier deescalation of empiric therapy for inpatients with methicillin-sensitive *Staphylococcus aureus* (MSSA) and vancomycin-resistant *Enterococcus* (VRE) bacteremia. The algorithm design focused on lessening the demand for pharmacist time by using electronic communications where possible. Our study compared inpatients with MSSA and VRE bacteremia from the time period before (pre-BC-GP) and after (post-BC-GP) implementation of the assay on June 25, 2013. The time from blood draw to identification and susceptibility results was decreased by 36.4 hours ($P < 0.001$) in the post-BC-GP group. The mean time from collection to the first dose of optimal antibiotics was reduced in the post-BC-GP group by 18.9 hours ($P = 0.004$) overall, with a 20.6-hour reduction ($P = 0.009$) for patients with MSSA and a 20.7-hour reduction ($P = 0.077$) for patients with VRE. Additionally, the percent of patients on empiric therapy who were placed on optimal antibiotics at any time after the Gram stain result was available increased from 64% (45/70) pre-BC-GP to 80% (43/54) post-BC-GP. The BC-GP led to an increased rate of deescalation of empiric antibiotics and a reduction in the time to optimal antibiotics for patients with MSSA and VRE bacteremia.

A variety of tests can identify organisms directly from positive blood culture bottles. These include matrix-assisted laser desorption/ionization time of flight (1), DNA hybridization (2), and polymerase chain reaction (3, 4). The Verigene Gram-Positive Blood Culture (BC-GP) assay (Nanosphere, Inc., Northbrook, IL) is a multiplex, DNA hybridization assay that detects 3 genera, 9 species, and 3 resistance markers directly from blood cultures positive for gram-positive organisms. It takes 2.5 hours to produce results.

This study focused on the impact of implementing the rapid detection of methicillin-sensitive *Staphylococcus aureus* (MSSA) and vancomycin-resistant *Enterococcus* (VRE) using the Verigene BC-GP test on patients with these two organisms. The primary objective was to measure the reduction in time from blood culture collection to the first dose of optimal antibiotics. We also assessed the length of hospital stay for patients before and after implementation of the BC-GP for survivors.

METHODS

This was a single-center, retrospective, nonrandomized comparison before and after an intervention for patients admitted with MSSA and VRE bacteremia to Baylor University Medical Center at Dallas (BUMC), a 1079-bed tertiary referral center. Blood cultures were performed at the affiliated reference laboratory, med fusion, in Lewisville, Texas, which is approximately 20 miles from BUMC. All patients with MSSA bacteremia from December 15, 2012, to December 13, 2013, or VRE bacteremia from October 21, 2012, to December 13, 2013, were included in the study unless they met one of three exclusion criteria (Figure 1), which included 1) patients who were not admitted and patients who expired or were discharged before blood culture results were available; 2) patients with blood culture reports that were corrected after they were finalized; and 3) patients who did not have the BC-GP done on their blood culture after the test had been implemented (these samples were inadvertently omitted). The BC-GP went live on June 25, 2013. Patients who had blood cultures prior to the implementation of the BC-GP were in the pre-BC-GP group; those whose blood cultures occurred after implementation were in the post-BC-GP group. This study was approved by the BUMC institutional review board.

Patients were identified by searching the laboratory's database for the target organisms. Patients were included more than once if they had two separate bacteremic episodes, which was defined as >1 month from the last positive blood culture or a separate admission that occurred >30 days after discharge from the previous admission. Clinical data were obtained from the patient's electronic health record (EHR). Data collected included demographic characteristics, intensive care unit (ICU) admission, and antibiotic therapy. Comorbidities were identified if they were documented in the problem list section of

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Figure 1. Eligibility and inclusion of bacteremic episodes. The most common reasons for ineligibility were death or discharge prior to the availability of the index blood culture results. MSSA indicates methicillin-sensitive *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*; LOS, length of stay.

the EHR. For patients admitted to the ICU for some or all of their hospital stay, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score was calculated based on the characteristics during the 24 hours following ICU admission.

Times were documented from blood culture collection to the following: Gram stain, BC-GP result (in the postimplantation group), traditional identification and susceptibilities, and the first dose of optimal antibiotics. Fourteen patients were already receiving the optimal antimicrobials at the time of the Gram stain and were not included in the time to optimal an-

tibiotic analysis. Patients who received the optimal antibiotic >200 hours from the blood culture draw were also not included, as we believed that this change was likely not in response to the blood culture result. Patients who died during their hospital admission were not included in the length of hospital stay analysis.

Antibiotics were documented based on the date and time that the dose was given as recorded in the medication administration record. For MSSA, optimal antimicrobials were considered to be oxacillin, nafcillin, or cefazolin. For VRE, optimal antimicrobials included daptomycin or linezolid.

Blood cultures during the pre-BC-GP and post-BC-GP periods were processed identically. Blood was collected in a BacTAlert FA (30 mL) and/or FN (40 mL) bottle (bioMérieux, Durham, NC) and transported via courier to med fusion. Couriers picked up specimens from BUMC every 2 hours, and the time to drive from BUMC to med fusion was 30 to 60 minutes. Upon arrival at med fusion, bottles were incubated on the BacTAlert automated blood culture system for up to 5 days. When the aerobic or anaerobic bottle was identified as positive, a Gram stain was performed, and the media were inoculated on appropriate solid agar media. Plates were read after approximately 24 hours of incubation, at which time rapid biochemical tests, such as coagulase, catalase, and pyrrolidonyl arylamidase (PYR, Remel, Lenexa, KS), were performed and the identification was released in the EHR. Identification and susceptibility testing were performed using traditional phenotypic methods and the VITEK®2, (bioMérieux). During the post-BC-GP period, the first bottle per bacteremic episode that showed gram-positive cocci was tested using the BC-GP according to the package insert (2). The BC-GP was also run if the Gram stain showed gram-positive cocci mixed with organisms of other Gram morphologies. The BC-GP was run 24 hours a day, 7 days a week.

Reporting occurred per routine protocol, as described below, with modification during the post-BC-GP period. Critical calls from med fusion to BUMC are required to take place within 30 minutes from the time the result is available. BUMC's critical call procedure for inpatients consists of calling the nurse on the ward within 15 minutes, who is responsible for telling the physician. Before implementation of the BC-GP (pre-BC-GP), critical calls were made at the time of the Gram stain. Blood cultures that were identified as VRE were also called as critical values. These results were also released in the EHR.

In the post-BC-GP period, the above procedure continued. In addition to calling in the BC-GP results as a critical value to the nurse on the floor (who was responsible for telling the physician), the results were released in the EHR. In the EHR, the BC-GP result for MSSA was accompanied by an interpretive comment describing a recommendation for treatment. The comment stated, "*Staphylococcus aureus*. MSSA—consider switching to oxacillin or cefazolin if no severe beta-lactam allergy. Recommended by BUMC Stewardship. Tested by Verigene Molecular Assay." There was no comment for VRE. The comment for MSSA and other organisms tested by the BC-GP underwent a rigorous approval process by the Antimicrobial Stewardship Program (ASP), infectious disease physicians, and laboratory staff.

Patient characteristics and clinical outcomes were compared between the pre- and post-BC-GP groups. Student's *t* test was used for comparison of continuous variables. The chi-square test and Fisher's exact test were used for categorical variables.

RESULTS

A total of 168 episodes of bacteremia were screened, including 126 with MSSA and 42 with VRE. Eleven patients in the pre-BC-GP group and 10 in the post-BC-GP group met exclusion criteria (Figure 1). Eighty episodes of bacteremia (59 with MSSA and 21 with VRE) were included in the analysis in the pre-BC-

Table 1. Demographics and baseline characteristics for patients in the pre- and post-gram-positive blood culture study groups

Characteristic	Implementation of gram-positive blood culture	
	Before (n = 80)	After (n = 67)
Organism		
MSSA	59 (74%)	51 (76%)
VRE	21 (26%) ^a	16 (24%) ^b
Age, years	53.2 ± 17.4 ^c	55.5 ± 16.2
Male sex	47 (59%)	41 (61%)
Allergies		
Penicillin	15 (19%)	15 (22%)
Vancomycin	4 (5%)	3 (5%)
Comorbid conditions		
Diabetes	34 (43%)	21 (31%)
Chronic pulmonary disease	7 (9%)	13 (19%)
Cerebrovascular disease	7 (9%)	2 (3%)
Chronic kidney disease	7 (9%)	13 (19%)
Cirrhosis	9 (11%)	14 (21%)
HIV/AIDS	5 (6%)	3 (5%)
Cardiovascular disease	10 (13%)	8 (12%)
Surgery in previous 30 days	5 (6%)	6 (9%)
Solid organ transplant	3 (4%)	6 (9%)
Bone marrow transplant	5 (6%)	4 (6%)
Malignancy		
Solid tumor	5 (6%)	2 (3%)
Hematologic malignancy	6 (8%)	4 (6%)
ICU admission ^d	30 (38%)	31 (46%)
APACHE II ^e score, mean	20.5 ± 7.8	20.8 ± 7.3
Days in ICU	10.5 ± 10.1	11.6 ± 12.3
Polymicrobial infections	8 (10%)	6 (9%)
Race		
White	46 (58%)	44 (66%)
Black	22 (28%)	16 (24%)
Hispanic	7 (9%)	6 (9%)
Other	5 (6%)	1 (2%)

^aIncludes 18 vancomycin-resistant *Enterococcus faecium* and 3 vancomycin-resistant *E. faecalis*.

^bIncludes 15 monomicrobial vancomycin-resistant *E. faecium* and 1 polymicrobial vancomycin-resistant *E. faecalis* found with *E. faecium* and other organisms.

^cAll ± values are means plus/minus the standard deviation.

^dIncludes patients with ICU admission any time during the index hospital admission.

^eThe APACHE II score was calculated based on the characteristics during the initial 24 hours following ICU admission. Missing variables were considered normal.

MSSA indicates methicillin-sensitive *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit.

GP group; 67 (51 with MSSA and 16 with VRE) were included in the post-BC-GP group (Figure 1). There were no statistically significant differences in the pre and post groups with regards to demographic data (Table 1). There were 14 polymicrobial cultures (8 pre- and 6 post-BC-GP).

Figure 2. Timeline comparison of blood culture results in the pre- and post-BC-GP study periods. All times are listed as the mean $\pm$ standard deviation in hours. ID indicates identification; BC-GP, gram-positive blood culture.

From the time of the blood draw, the Gram stain was reported an average of 23.4 ± 10.0 hours in the pre-BC-GP group and 22.3 ± 10.0 hours in the post-BC-GP group (Figure 2). In the pre-BC-GP group, the preliminary identification was reported at 41.0 ± 13.4 hours, and the final identification and susceptibility results were reported at an average of 61.7 ± 17.0 hours. In the post-BC-GP group, the BC-GP result was called to the floor and released in the EHR an average of 25.3 ± 10.1 hours following the blood draw, which was an average of 3.1 ± 1.1 hours following the Gram stain result. Seventy patients (88%, 70/80) in the pre-BC-GP group and 54 patients in the post-BC-GP group (81%, 54/67) were on empiric vancomycin. The percent of these patients that were later placed on optimal antibiotics after the Gram stain result and during the bacteremic episode (within 200 hours from the blood draw) increased from 64% (45/70) pre-BC-GP to 80% (43/54, $P = 0.011$) post-BC-GP.

For patients who were not on optimal antibiotics (regardless of empiric vancomycin use) by the time of the Gram stain, the average time from blood culture collection to the first dose of optimal antibiotics was 66.2 ± 29.35 hours pre-BC-GP ($n = 54$) and 47.3 ± 36.0 hours post-BC-GP ($n = 51$). For MSSA, the average times were 71.9 ± 23.2 hours pre-BC-GP ($n = 34$) and 51.3 ± 38.9 post-BC-GP ($n = 38$). For VRE, the average times were 56.3 ± 26.2 hours pre-BC-GP ($n = 20$) and 35.6 ± 23.0 post-BC-GP ($n = 13$). The mean time from collection to the first dose of optimal antibiotics was reduced overall in the post-BC-GP group by 18.9 hours ($P = 0.004$), with a 20.6-hour reduction ($P = 0.009$) for patients with MSSA and a 20.7-hour reduction ($P = 0.08$) for patients with VRE.

In-hospital mortality rates during the index admission were 16.3% (13/80) for the pre-BC-GP group and 26.9% (18/67) for the post-BC-GP group ($P = 0.16$). Patients who died during their hospital admission were not included in the length of

stay analysis. For survivors, the average length of stay was 19.7 ± 21.8 days pre-BC-GP ($n = 67$) and 17.6 ± 14.1 days post-BC-GP ($n = 49$, $P = 0.56$). For MSSA survivors, the average length of stay was 14.6 ± 13.7 days ($n = 52$) in the pre-BC-GP group and 15.1 ± 12.6 days in the post-BC-GP group ($n = 41$, $P = 0.88$). For VRE survivors, the average length of stay was 37.3 ± 33.7 days ($n = 15$) in the pre-BC-GP group and 30.8 ± 14.9 in the post-BC-GP group ($n = 8$, $P = 0.61$).

DISCUSSION

Our study found a decrease in time from blood draw to identification and susceptibility results of 36 hours ($P < 0.001$) after implementation of the BC-GP. Overall, we found that patients in the post-BC-GP group obtained the first dose of optimal antibiotics 19 hours faster; additionally, more of these patients received optimal antibiotics. Other studies have shown that rapid identification of organisms in blood cultures has many benefits, such as faster time to optimal antimicrobials (5–7), decreased length of hospital stay (7), and decreased overall hospital costs (5, 7, 8).

Current literature suggests that the benefits of a faster time to antibiotic therapy with decreased time to identification rely on real-time involvement, most commonly by a clinical pharmacist or another member of an active ASP (5–9). Frye et al (9) reported that following implementation of a rapid blood culture test, there was no reduction in the time to optimal antibiotics for patients with MSSA in spite of a decrease in time to result. The authors attributed this to the fact that results were only passively released into their EHR and no additional interventions were made at the time of identification of MSSA. On the contrary, Bauer et al (8) showed that patients with MSSA received nafcillin or cefazolin 1.7 days ($P = 0.002$) sooner with the use of a rapid polymerase chain reaction and an active ASP. In their study, the microbiology laboratory notified both the

physician and an infectious disease pharmacist with the assay result. However, the pharmacist was only contacted between 8:00 am and 5:00 pm Monday through Friday. In our study, we showed that patients received optimal antibiotics about 1 day earlier, without the need for a real-time, active intervention by a pharmacist. Our use of antimicrobial recommendation comments accompanying the BC-GP result demonstrated that up-front planning and communication among infectious disease physicians, the ASP, and the lab had benefits that equaled other institutions' use of real-time interventions. Finally, the use of these comments was not restricted to any day or time, nor were they subject to any particular person's ability and availability to communicate with care providers.

Although other studies about rapid blood cultures have shown a decrease in the length of stay (7), our study did not find a statistically significant difference. Our study included patients with infections in other organ systems and polymicrobial infections and patients with serious comorbidities; other studies have excluded these patients.

The in-hospital mortality rates in each group were not statistically different. The pre-BC-GP group was hospitalized in the winter and spring (December to June) and the post-BC-GP group was hospitalized in the summer and fall (June to December); seasonal differences could have affected the underlying disease. Polymicrobial infections accounted for 9.5% of bacteremic episodes included in the study. Pavlaki et al (10) showed that polymicrobial infection is a significant contributor to 28-day mortality.

Numerous studies have shown that delayed time to or lack of optimal antibiotic use increases morbidity and mortality. Lodise et al (11) reported that delayed treatment (>44.75 hours from the time the culture result was available) of *Staphylococcus aureus* bacteremia led to a 7-day longer hospital stay (20.2 days vs. 14.3 days; $P = 0.05$) and was an independent predictor of infection-related mortality. Ibrahim et al (12) showed that in-hospital mortality was greater in ICU patients who received inadequate antimicrobial therapy (61.9% vs. 28.4%, $P < 0.001$). Inadequate antibiotic use was an independent determinant of hospital mortality. In their study, the organisms with the highest rates of inappropriate antimicrobial therapy included VRE ($n = 17$; 100%), *Candida* species ($n = 41$; 95.1%), and MRSA ($n = 46$; 32.6%). Although statistically significant changes in length of stay and mortality were not seen in our study, we can presume that the patients who received optimal antibiotics faster would have better clinical outcomes.

One limitation of this study is that it looked at only 2 of the 12 organisms that are detected by the BC-GP. Furthermore, our study was not powered to assess long-term outcomes such as crude mortality or readmission rates. Our study attempted to reflect real life, so patients with polymicrobial bloodstream infections and other infections were included. We did not exclude patients with comorbidities that are often associated with a long length of stay. We also did not exclude or differentiate among patients with allergies to any of the antibiotics referred to in the study, as patients with documented allergies to those

antibiotics are sometimes still treated with them based on the care provider's clinical judgment. Our study calculations utilized the time that the medication was administered and not the time that the medication was ordered.

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