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Impact of a Rapid Microarray-Based Assay for Identification of Positive Blood Cultures for Treatment Optimization for Patients with Streptococcal and Enterococcal Bacteremia

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Implementation of the Verigene Gram-positive blood culture test led to reductions in time to acceptable antibiotic overall (1.9 versus 13.2 h, respectively; $P = 0.04$) and time to appropriate antibiotic for patients with vancomycin-resistant *Enterococcus* (4.2 versus 43.7 h; $P = 0.006$) and viridans group *Streptococcus* (0.2 versus 7.1 h; $P = 0.02$).

Enterococci and streptococci are frequent causes of bloodstream infections (BSIs), which are associated with high mortality when inappropriately treated (1). Timely initiation of appropriate antibiotics is vital, as this permits effective targeting of causative pathogens, decreased antimicrobial exposure, and possible cost savings. Therefore, rapid molecular tests are being used with increasing frequency to facilitate antimicrobial stewardship efforts. The FDA-cleared Verigene Gram-positive blood culture test (BC-GP) (Nanosphere, Inc., Northbrook, IL) detects bacterial DNA from blood cultures positive for *Staphylococcus*, *Streptococcus*, *Enterococcus*, and *Listeria* spp. It also identifies *mecA*, which confers methicillin resistance in staphylococci, and *vanA* and *vanB* genes, which confer vancomycin resistance in enterococci.

We previously published a targeted treatment algorithm based on BC-GP results (2). In this study, we evaluated clinical outcomes associated with implementation of the BC-GP technology and targeted treatment algorithm in patients with streptococcal and enterococcal bacteremia in comparison with traditional microbiological methods. The primary outcome was time to appropriate antibiotic. Secondary outcomes included time to acceptable antibiotic, time to culture clearance, length of stay (LOS), and mortality.

This study, approved by the University of North Carolina Institutional Review Board, used a quasiexperimental design comparing pre- and postintervention groups over 17 months. Patients with blood cultures positive for Gram-positive cocci (GPC) in pairs and/or chains were included. Subjects were excluded if they had polymicrobial blood cultures, had positive cultures for *Streptococcus* or *Enterococcus* spp. in both the case and control periods, or were still hospitalized or if the positive blood culture was classified as a contaminant (i.e., one bottle positive for viridans group streptococci [VGS]). Additionally, if a subject had a second blood culture that was positive for the same organism within 14 days of the first culture, the second culture was excluded.

In the preintervention period, Gram stain results were documented in the electronic medical record (EMR) system and phoned to the patient's primary team. After BC-GP implementation, Gram stain results were still phoned to the primary team; however, if the stain was positive for GPC in pairs and/or chains, the BC-GP test was performed. The result was communicated by microbiology laboratory staff to the pharmacist on call, who referred to a treatment algorithm based on local susceptibility patterns and clinical guidelines to recommend targeted therapy (2). BC-GP results were confirmed by conventional microbiological methods (matrix-assisted laser desorption ionization–time of flight mass spectrometry [MALDI-TOF MS] and Vitek2; bioMérieux, Durham, NC).

The EMR was used to determine the time to appropriate and acceptable therapy. Appropriate therapy was defined as an antibiotic delineated in the algorithm. Acceptable therapy was defined as an antibiotic that provided adequate activity against the organism identified but was not the therapy of choice. If appropriate or acceptable therapy was received before the positive Gram stain, the time was 0 days. These data were collected retrospectively by systematic chart review.

Univariate analysis was performed using a *t* test for continuous variables and a Pearson χ^2 test for categorical variables. *P* values were not calculated if there were fewer than 5 subjects in either the pre- or post-BC-GP group. A two-tailed *P* value of <0.05 was considered significant (SAS v9.3; SAS Institute, Cary, NC).

In the study period, 205 subjects were identified. After exclusion criteria were applied, 74 cases and 65 controls remained. Baseline demographics, laboratory values, and risk factors for bacteremia were not different between groups (Table 1). Organisms identified by the BC-GP test and traditional culture were not sta-

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TABLE 1 Baseline demographics

Characteristic[a]	Value for group		*P* value
	Pre-BC-GP ($n = 65$)	Post-BC-GP ($n = 74$)	
Age [mean (SD)]	54.5 (22.0)	57.3 (20.8)	0.43
No. (%) with malignancy	27 (41.5)	32 (43.2)	0.84
Solid organ tumor	14 (21.5)	21 (28.4)	0.35
Hematologic malignancy	14 (21.5)	14 (18.9)	0.70
HSCT	8 (12.3)	3 (4.1)	0.07
No. (%) with solid organ transplant recipient	2 (3.1)	4 (5.4)	0.50
No. (%) diabetic	17 (26.2)	28 (37.8)	0.14
No. (%) HIV positive	1 (1.5)	2 (2.7)	0.64
No. (%) with recent surgery within 1 mo	12 (18.5)	11 (14.9)	0.57
No. (%) with systemic steroids	8 (12.3)	10 (13.5)	0.83
No. (%) with immunomodulating agents[b]	13 (20.0)	13 (17.6)	0.71
No. (%) with dialysis	6 (9.2)	6 (8.1)	0.81
No. (%) neutropenic (ANC < 0.5)	13 (20.0)	11 (14.9)	0.42
Mean (SD) ANC for neutropenic patients	0.08 (0.19)	0.13 (0.18)	
No. (%) with renal failure (serum creatinine > 2)	17 (26.2)	16 (21.6)	0.53
No. (%) with hepatic failure	9 (13.9)	6 (8.1)	0.28
No. (%) in intensive care unit	6 (9.2)	10 (13.5)	0.43
No. (%) with TPN	6 (9.2)	3 (4.1)	0.22
No. (%) with endocarditis proven by ECHO	4 (8.9)	9 (18.0)	0.20
No. (%) with central catheter	28 (43.1)	26 (35.1)	0.34

[a] HSCT, hematopoietic stem cell transplant; TPN, total parenteral nutrition.
[b] Immunomodulating agents include tacrolimus, mycophenolate, cyclosporine, azathioprine, sirolimus, or other transplant biologics.

tistically different, with VGS and vancomycin-susceptible *Enterococcus faecalis* (VSE) being the most common (Table 2).

Mean time to appropriate antibiotic was numerically but not statistically shorter in the post-BC-GP group than the pre-BC-GP group (4.5 versus 10.2 h, respectively; $P = 0.07$). The largest difference was seen in patients with vancomycin-resistant *Enterococcus* (VRE), where the time to appropriate antibiotic was 4.2 versus 43.7 h, respectively ($P = 0.006$). A significant difference was also seen in patients with VGS (0.2 versus 7.1 h; $P = 0.02$). No significant difference was observed in patients with VSE (0.7 versus

TABLE 2 Organisms identified by culture

Organism	No. (%) in group		*P* value
	Before BC-GP ($n = 65$)	After BC-GP ($n = 74$)	
Group A *Streptococcus*	3 (4.6)	1 (1.4)	0.25
Group B *Streptococcus*	3 (4.6)	11 (14.9)	0.05
Streptococcus anginosus group	2 (3.1)	5 (6.8)	0.32
Viridans group *Streptococcus*	17 (26.2)	15 (20.3)	0.41
Streptococcus pneumoniae	8 (12.3)	10 (13.5)	0.83
Other *Streptococcus* spp.	6 (9.2)	4 (5.4)	0.38
Enterococcus faecalis			
Vancomycin susceptible	14 (21.5)	15 (20.3)	0.85
Vancomycin resistant	0 (0)	0 (0)	NA[a]
Enterococcus faecium			
Vancomycin susceptible	4 (6.2)	4 (5.4)	0.85
Vancomycin resistant	7 (10.8)	7 (9.5)	0.80
Other	1 (1.5)	2 (2.7)	0.64

[a] NA, not applicable.

TABLE 3 Mean time to appropriate and acceptable antibiotic

Parameter	Mean (SD) value for group		*P* value	*n*	
	Pre-BC-GP	Post-BC-GP		Pre-BC-GP	Post-BC-GP
No. (%) that never received appropriate antibiotic	11 (16.9)	8 (10.8)	0.30		
Mean time to appropriate antibiotic (h), by organism	10.2 (19.8)	4.5 (14.4)	0.07	54	66
Group A *Streptococcus*	17.0 (23.8)	6.6 (NA[c])	NA	2	1
Group B *Streptococcus*	0 (0)	15.8 (20.3)	NA	2	8
Streptococcus anginosus group	2.4 (NA)	50.9 (65.4)	NA	1	2
Viridans group *Streptococcus*	7.1 (10.7)	0.2 (0.5)	0.02	12	14
Streptococcus pneumoniae	1.1 (1.4)	1.4 (3.9)	0.85	6	10
Other *Streptococcus* spp.	10.3 (21.9)	0.4 (0.3)	NA	6	3
E. faecalis					
Vancomycin susceptible	2.2 (6.3)	0.7 (1.3)	0.35	14	15
Vancomycin resistant	NA	NA	NA	0	0
E. faecium					
Vancomycin susceptible	7.4 (10.6)	0.9 (0.9)	NA	3	4
Vancomycin resistant	43.7 (31.5)	4.2 (2.8)	0.006	7	7
Mean time to appropriate antibiotic (h), by treatment group					
Penicillin susceptible *Streptococcus*[a]	7.3 (14.9)	21.3 (30.6)	0.35	5	11
Vancomycin susceptible *Streptococcus*[b]	6.4 (13.1)	0.7 (2.4)	0.03	24	27
Vancomycin susceptible *Enterococcus*	3.2 (7.1)	0.7 (1.2)	0.15	17	19
Vancomycin resistant *Enterococcus*	43.7 (31.5)	4.2 (2.8)	0.006	7	7
Mean time to appropriate antibiotic (h) by genus					
All *Streptococcus* spp.	6.6 (13.1)	6.7 (18.6)	0.98	29	38
All *Enterococcus* spp.	15.0 (25.4)	1.7 (2.3)	0.01	24	26
No. (%) that never received acceptable antibiotic	1 (1.5)	1 (1.4)	0.93		
Mean time to acceptable antibiotic (h), by organism	13.2 (46.0)	1.9 (7.2)	0.04	64	73
Group A *Streptococcus*	21.1 (18.2)	5.6 (NA)	NA	3	1
Group B *Streptococcus*	0 (0)	6.3 (17.6)	NA	3	11
S. anginosus group	1.2 (1.7)	0.9 (2.1)	NA	2	5
Viridans group *Streptococcus*	8.6 (11.7)	0.1 (0.3)	0.01	16	14
Streptococcus pneumoniae	0.6 (1.3)	1.3 (4.0)	0.66	8	10
Other *Streptococcus* spp.	1.2 (2.4)	0 (0)	NA	6	4
Enterococcus faecalis					
Vancomycin susceptible	2.2 (6.3)	0.7 (1.3)	0.35	14	15
Vancomycin resistant	NA	NA	NA	0	0
Enterococcus faecium					
Vancomycin susceptible	94.7 (174.7)	0.9 (0.9)	NA	4	4
Vancomycin resistant	30.8 (26.6)	4.2 (2.8)	0.02	7	7

[a] Group A *Streptococcus*, group B *Streptococcus*, and *S. anginosus* group.
[b] Viridans group *Streptococcus* spp. (not *S. anginosus* group), *S. pneumoniae*, and other *Streptococcus* spp.
[c] NA, not applicable.

3.2 h; $P = 0.15$). For time to acceptable antibiotic, the overall mean time was 11 h shorter in the post-BC-GP group (1.9 versus 13.2 h, respectively; $P = 0.04$) (Table 3).

Nonsignificant decreases in patient outcomes such as time to culture clearance and LOS were observed in the post-BC-GP group. There was no difference in mortality, which was approximately 10% in both groups ($P = 0.82$).

To our knowledge, this is the first study investigating the clinical impact of a rapid molecular assay on patients with streptococcal bacteremia. Two prior studies evaluated the impact of rapid detection methods on patients with enterococcal bacteremia (3, 4). Forrest and colleagues (3) examined the impact of the PNA FISH (peptide nucleic acid fluorescence in situ hybridization) test (AdvanDx, Inc., Woburn, MA) on outcomes in patients with enterococcal bacteremia and found that patients in the postintervention group received appropriate therapy significantly faster, resulting in decreased mortality (26% versus 45%; $P = 0.04$) but no difference in LOS. Sango and colleagues (4) also investigated the impact of the BC-GP assay on patients with enterococcal bacteremia. A significant difference was observed in time to appropriate therapy in patients with VRE (31.6 versus 62.7 h; $P < 0.001$) but not VSE (18.6 versus 40.2 h; $P = 0.1145$). Total hospital LOS was not improved by the test (43.5 versus 22.2 days; $P = 0.141$) when deceased patients were removed from the analysis.

Explanations for the lack of significant difference in the primary outcome include the fact that our institution is an academic

medical center that provides care for many immunocompromised populations; therefore, it may not have been feasible to narrow empirical antimicrobial therapy despite targeted culture results. Additionally, providers may have opted to wait for final confirmation of results.

Limitations of the study include that it was conducted at a single center with a small sample size and was limited by the number of cases that occurred. Many subjects were excluded due to polymicrobial blood cultures ($n = 62$). Several patients were on appropriate or acceptable therapy before the BC-GP result due to empirical treatment. The study does not control for the stewardship intervention itself; therefore, it is impossible to know if differences observed were a product of the technology, stewardship, or both.

In conclusion, minimizing time to targeted antimicrobial therapy may reduce exposure to broad-spectrum antibiotics and decrease costs. Utilization of rapid molecular assays, such as the BC-GP test, in conjunction with antimicrobial stewardship programs, can decrease the time to targeted therapy, especially in patients with VRE.

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