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Real-world performance of a microarray-based rapid diagnostic for Gram-positive bloodstream infections and potential utility for antimicrobial stewardship

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ABSTRACT

The Verigene Gram-positive blood culture assay (BC-GP) is a microarray-based rapid diagnostic test, which includes targets for 12 bacterial species and 3 resistance determinants. We prospectively compared the diagnostic accuracy of the BC-GP to routine microbiologic methods and evaluated the potential of the BC-GP for antimicrobial stewardship programs. A total of 143 consecutive patients with Gram-positive bacteremia were included in the analysis. BC-GP correctly identified 127/128 (99.2%) of organisms from monomicrobial blood cultures and 9/14 (64.3%) from polymicrobial, including all methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci. Stewardship interventions were possible in 51.0% of patients, most commonly stopping or preventing unnecessary vancomycin or starting a targeted therapy. In Monte Carlo simulations, unnecessary antibiotics could be stopped at least 24 hours earlier in 65.6% of cases, and targeted therapy could be started at least 24 hours earlier in 81.2%. BC-GP is a potentially useful test for antibiotic stewardship in patients with Gram-positive bacteremia.

1. Introduction

Gram-positive bacteria account for over 50% of all nosocomial bloodstream infections in the United States, with methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) accounting for roughly 25% of all isolates (Wisplinghoff et al., 2004). Overall mortality in patients with Gram-positive bacteremia ranges from 10% to 40%, with delays in effective antimicrobial therapy leading to a dramatic increase in mortality (Lautenbach et al., 1999; van Hal et al., 2012). Patients with Gram-positive bacteremia also often suffer from substantial long-term morbidity as a result of prolonged hospitalization and generalized deconditioning.

Relying exclusively on traditional microbiological techniques, final identification and antimicrobial susceptibility testing can take 2–3 days following Gram stain identification of a Gram-positive bacterial isolate. Patients with Gram-positive bacteremia are therefore often treated with broad-spectrum antimicrobial agents, such as vancomycin, until the final sensitivity results are known. While this strategy provides an antibiotic that is active against the most likely causative agents, patients with methicillin-susceptible *S. aureus* (MSSA) treated with vancomycin are known to have increased mortality in comparison to those treated with a β-lactam (Lodise et al., 2007; Stryjewski et al., 2007).

Rapid diagnostic tests (RDTs) are an increasingly common method by which clinical microbiology laboratories improve on the time delays associated with traditional culture methodologies. Additionally, hospital-based antimicrobial stewardship teams are able to utilize the results of RDTs to increase the efficacy of antibiotics, while minimizing toxicity and decreasing the overall cost of care (Goff et al., 2012; MacDougall and Polk, 2005). Several RDTs have entered routine clinical use, including matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS), peptide nucleic acid fluorescence *in situ* hybridization, polymerase chain reaction (PCR), or other molecular-based tests. The Verigene Gram-positive blood culture (BC-GP) assay (Nanosphere, Northbrook, IL, USA) uses a microarray-based technology that allows for species-level identification and identification of resistance gene determinants for the most common clinically relevant Gram-positive bacteria, with a turnaround time of roughly 2.5 hours (Buchan et al., 2013). BC-GP includes targets for species-level identification of *Enterococcus faecalis, Enterococcus faecium, S. aureus, Staphylococcus epidermidis, Staphylococcus lugdunensis, Streptococcus anginosus* group, *Streptococcus agalactiae, Streptococcus pneumoniae*, and *Streptococcus pyogenes* as well as genus-level identification of other staphylococci, streptococci, and *Listeria*. Additionally, the panel detects the resistance genes *mecA, vanA*, and *vanB*. The ability of the BC-GP to supplement routine antimicrobial stewardship efforts is largely unknown. We performed a prospective cohort study to establish the

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real-world performance characteristics of BC-GP in comparison to routine clinical microbiological work-up and to establish the potential role of BC-GP in antimicrobial stewardship.

2. Materials and methods

2.1. Patient identification and eligibility

Hospitalized patients with blood cultures submitted as part of routine clinical care to a 650-bed tertiary care hospital were eligible for inclusion in this study. All blood cultures with Gram stain identification of Gram-positive cocci between October and December 2013 were prospectively screened for eligibility. To be included in the study, patients were required to be inpatients aged >18 years of age at the time of screening. Patients were excluded from the study if they had previously been tested using the BC-GP. This study was approved by the University of Houston Committee for the Protection of Human Subjects with a waiver of informed consent.

2.2. Blood culture processing

Blood cultures were processed according to routine clinical laboratory practices. Blood cultures were obtained using BacT/ALERT (bioMérieux, Durham, NC, USA) aerobic (FA) and anaerobic (SN) blood culture bottles and incubated in the BacT/ALERT 3D (bioMérieux) automatic monitoring system. Bottles flagged as positive were initially tested using routine Gram staining. In cases where a trained microbiology technician was unavailable for performance of Gram staining, positive bottles were removed from the BacT/ALERT 3D system to await Gram stain identification. Standard laboratory procedures were used for species identification including catalase and coagulase testing for suspected and staphylococci and bile esculin, optochin, pyrrolidonyl arylamidase (PYR), and serologic typing for suspected streptococci or enterococci. For coagulase-negative staphylococci and viridans group streptococci, antimicrobial sensitivity testing (AST) was performed only for certain organisms based on the ratio of positive blood cultures or upon clinician request. For all other organisms, an automated system (Vitek 2; bioMérieux) was used for species-level identification and AST testing. No additional testing or identification was performed on coagulase-negative staphylococci and viridans group streptococci solely for purposes of this study.

2.3. Nanosphere BC-GP

All testing on the Verigene BC-GP was performed according to manufacturer's instructions (Nanosphere Inc., 2012). Briefly, the BC-GP identifies molecular target through DNA extraction and subsequent hybridization to complementary oligonucleotides present on the microarray grid. A secondary oligonucleotide affixed to a gold nanoparticle is then hybridized to captured bacterial DNA, and the target is identified through analysis of the relative optical density of the probes on the panel. Total hands-on time was approximately 10 minutes with a 2.5-hour test run time. Testing using the BC-GP was performed in batches the day following determination of eligibility for inclusion in the study. In cases where more than 1 blood culture bottle was positive, only 1 bottle was chosen for testing with the BC-GP.

2.4. Determination of utility in antimicrobial stewardship

At the study hospital, the primary treatment team was notified *via* phone call at the time of Gram stain identification of any positive blood cultures within 15 minutes of a positive result. Additionally, routine clinical care of patients with bacteremia included mandatory consultation by the hospital's antimicrobial stewardship service by a daily review of a list containing all positive blood culture results. Infectious diseases physician consultation was obtained at the discretion of the primary treatment team. During the period of this validation study, hospital clinicians, including members of the antimicrobial stewardship service and infectious diseases consultants, were unaware of the BC-GP results unless it was determined that a pathogenic organism was being treated with inadequate therapy. No changes in the antimicrobial stewardship process or routine care occurred during the time period of this study.

To determine the potential impact of the BC-GP on antimicrobial stewardship efforts, a prospective audit was performed on each patient by a study investigator infectious diseases pharmacist and infectious diseases physician in accordance with the Infectious Disease Society of America/Society for Healthcare Epidemiology of America guidelines (Dellit et al., 2007; Palmer et al., 2011). Briefly, prospective audit involved a comprehensive clinical review of each patient by the infectious diseases trained pharmacist in consultation with the infectious disease physician to evaluate for opportunities to optimize antimicrobial treatment (e.g., alter or narrow antibiotic therapy, etc.) (MacDougall and Polk, 2005). Following discussion, potential interventions using results for the BC-GP for each patient were identified and recorded. Interventions not related to the BC-GP assay (e.g., narrowing or discontinuing therapy targeted at Gram-negative organisms) were not considered in this analysis. During this validation stage, potential interventions were documented, but no clinical interventions or recommendations were made to the treatment team based on these audits. After identification of Gram-positive species and antimicrobial susceptibility profile, patients were again reviewed to assess timing of any changes in antibiotic therapy, related diagnostic or therapeutic procedures, and hospital discharge. In the event that the BC-GP identified a pathogenic organism that was not being appropriately treated, the medical team was contacted and a recommendation for treatment was made.

2.5. Statistical analysis

BC-GP performance characteristics were compared to traditional biochemical and/or automated identification (i.e., Vitek 2) at the study hospital. Monomicrobial cultures were considered independently of polymicrobial cultures. Discrepant results were resolved by repeat testing on the Vitek 2 panel using a threshold of >95% confidence. Stewardship interventions were grouped into common categories and reported as percentages of eligible patients. Potential time differences in the discontinuation or initiation of antibiotics were simulated by using the difference between the last dose (in the cases of discon-

Table 1
Comparison of BC-GP to conventional techniques for monomicrobial cultures.

Organism	Verigene detected	Conventional
E. faecalis	2	2
E. faecium	3	3
VRE	2	2
S. aureus	25	26
MRSA	9	9
CoNS[a]	77	77
S. anginosus	2	2
S. agalactiae	6	6
S. pyogenes	2	2
S. pneumoniae	3	2
Other streptococci[b]	7	8
Not reported[c]	8	8
Total	135	136

CoNS = coagulase-negative staphylococci.

[a] Not identified to the species level routinely and are grouped for clarity. Includes organisms reported by BC-GP as *S. epidermidis* and *Staphylococcus* spp. One run of the BC-GP resulted in a user error and no valid results reported.

[b] Reported by BC-GP as *Streptococcus* spp. Identified by routine methods as viridans group streptococci (n = 5), *Streptococcus gallolyticus* (n = 2), and *Streptococcus gordonii* (n = 1).

[c] Not included on the BC-GP panel. Identified by routine methods as *Micrococcus* spp. (n = 4), diphtheroids (n = 2), *Stomatococcus* spp. (n = 1), and *Eggerthella lenta* (n = 1).