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Reliability of the Verigene system for the identification for Gram-positive Bacteria and detection of antimicrobial resistance markers from children with bacteremia☆

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ABSTRACT

Background: Targeted antimicrobial therapy can reduce morbidity in patients with sepsis. Molecular methodologies used in the clinical laboratory can provide information about infectious agents faster than traditional culture methods. Using molecular information to make clinical decisions more quickly has been shown to improve patient outcomes, and reduce length of stay and healthcare cost in adults. Its effect on pediatric care is less well described.
Methods: Blood cultures growing Gram-positive cocci or Gram-positive bacilli on Gram stain were evaluated by molecular and traditional methodologies. Results from the molecular platform, Luminex Verigene® Blood Culture – Gram-positive Panel (BC-GP) were compared to results from standard culture and susceptibility testing (Vitek™ MS, Vitek™, E-test®). Overall statistical agreement is evaluated.
Results: 1231 positive pediatric blood cultures grew single isolates detectable by the BC-GP panel. 899 were correctly identified to species, 282 to genus, 50 isolates were not detected. All organisms detected by BC-GP that grew in single isolate cultures were identified as the same organism by Vitek™ MS with the exception of 7 organisms.112 cultures were found to have polymicrobial growth of Gram-positive organisms. Excellent overall agreement was noted for antimicrobial resistance markers with only 5 samples displaying discordant results.
Discussion: In general, clinicians can use the identification and antimicrobial resistance marker data gained from Luminex Verigene® BC-GP with confidence to alter empiric coverage. Rare instances of disagreement with traditional culture data led to maintaining the empiric clinical approach and did not result in patient harm.

1. Background

Timely, targeted antimicrobial therapy is a key principle of antimicrobial stewardship, and can reduce morbidity in patients with sepsis and other serious bacterial infections (Rhodes et al., 2017). To narrow therapy from empiric broad-spectrum agents, clinicians must be confident of an etiologic agent's identity and resistance pattern. Recent studies have shown that molecular identification of bloodstream pathogens can provide critical data, such as organism identification and detection of genomic antimicrobial resistance markers, in fewer than 3 hours from blood culture positivity that would otherwise require an average of 40 hours using traditional culture and susceptibility testing (Beal et al., 2013; Beekmann et al., 2003; Box et al., 2015; Felsenstein et al., 2016; Kumar et al., 2006; Sango et al., 2013; Sullivan et al., 2014; Walker et al., 2016). Use of molecular methodology resulting in earlier transition to targeted antimicrobial therapy has improved patient outcomes, and reduced length of stay and healthcare costs (Barenfanger et al., 1999; Box et al., 2015; Felsenstein et al., 2016; Kumar et al., 2006; Sango et al., 2013; Sullivan et al., 2014; Walker et al., 2016).

Clinical experience using these newer molecular techniques in children undergoing evaluation for bacteremia is limited. Pediatric blood cultures need to be evaluated separately from adults because blood collection for culture at pediatric institutions are tailored to blood culture bottles meant for pediatric population. Safely obtaining blood from infants and young children requires blood cultures to be performed with blood volumes lower than blood cultures obtained from mature adults.

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In our study, we sought to describe agreement between molecular and traditional culture-based methods among a cohort of pediatric patients with positive blood cultures and its effect on clinical management.

2. Methods

We tested the Luminex Verigene® (Luminex Corporation, Austin, TX) system, which uses microarray technology to identify select microbes at the genera or species level and genetic antimicrobial resistance markers with a 350 μl aliquot of blood culture medium (Beal et al., 2013; Luminex Corporation, 2016). The Luminex Verigene® Blood Culture Gram-positive panel (BC-GP) can identify 3 genera (*Staphylococcus*, *Streptococcus*, and *Listeria*) and 9 organisms to the species level (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus lugdunensis*, *Streptococcus agalactiae*, *Streptococcus anginosus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Enterococcus faecalis*, and *Enterococcus faecium*). In addition, the BC-GP also detects 3 well-described genetic resistance markers (*mecA*, *vanA*, and *vanB*) known for antimicrobial resistance to clinically relevant antimicrobials of at least one corresponding Gram positive organism.

From January 2014 through December 2017, all first-time positive (no previous positive blood cultures within 3 days) clinical blood cultures that contained Gram-positive organisms were subjected to both Luminex Verigene® BC-GP and standard clinical laboratory culture identification and antimicrobial susceptibility testing in the Cincinnati Children's Hospital Medical Center Diagnostic Infectious Disease Testing Laboratory. When bacterial growth was detected in a blood culture specimen by the BD Bactec 9000 system (Beckon Dickinson, Franklin Lakes, NJ), Gram staining of an aliquot of the positive blood culture broth medium was performed. Samples showing Gram-positive cocci or Gram-positive bacilli were tested using the Verigene® BC-GP assay following manufacturer instructions. An additional aliquot of blood culture medium was inoculated to standard solid media culture. Culture positive isolates were identified using Vitek™ MS (MALDI-ToF; bioMerieux, France) and tested for phenotypic antimicrobial susceptibility using Vitek™2 antibiotic susceptibility panels and/or E-test® (bioMerieux, France). *Staphylococcus epidermidis* isolates were evaluated with Vitek™2 and/or E-test® only if deemed clinically significant (defined as isolated from two or more blood cultures from the same patient within 3 days). Positive blood cultures containing Gram negative organisms and tested with the Verigene® Blood culture – Gram negative (BC-GN) panel were excluded from this study (Fig. 1).

For patients ≤25 years old, the concordance between the BC-GP and traditional culture-based methodologies was determined using overall percent agreement and Cohen's κ coefficient with corresponding 95% confidence intervals (CI) (Hardin et al., 2017). A κ coefficient > 0.9 was used to indicate near perfect agreement. Overall agreement across bacterial species was compared using Fisher's Exact Test or χ^2 Test where appropriate. All analyses were performed using STATA v14.1 (College Station, TX).

To determine the potential clinical impact, if any, on the patients, patient charts were reviewed for all events of: 1. Single isolates with discordant identification or 2. Any polymicrobial cultures containing pathogens with different susceptibility patterns. A clinical effect was defined as a potentially ineffective antimicrobial choice and/or prolonged course, prolonged hospital stay, and procedures performed that otherwise may not have occurred with more accurate information. This study was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board.

Constraints of this study including limitations reported in the Luminex Verigene® package insert include: the assay is not approved for testing outside of the FDA cleared targets in the U.S. and false positive results due to cross reaction of *Streptococcus mitis/oralis* and *Streptococcus pneumoniae* which have homologous genetic material (Luminex Corporation, 2016).

3. Results

3.1. Bacterial Identification

From January 2014 through December 2017, 2115 positive blood cultures were processed on the Luminex Verigene®. Of the positive blood cultures among patients ≤25 years old, 1503 stained Gram positive, and 1231 grew single isolates detectable by the BC-GP panel (Fig. 1). Of the single isolate cultures containing organisms on the BC-GP panel, 899 were correctly identified to species, 282 to genus, and 50 isolates were not detected (Table 1). No differences were noted in the overall agreement of BC-GP and traditional methods in identification of *Enterococcus*, *Streptococcus*, or *Staphylococcus* species ($p = 0.08$). *S. aureus, E. faecium*, and *S. agalactiae*, were detected by

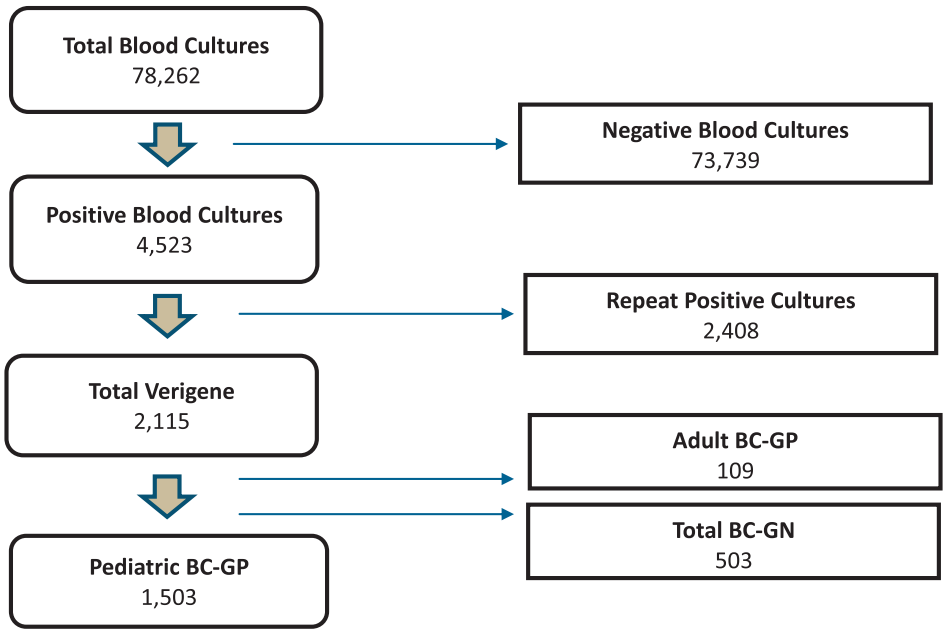

Fig. 1. Number of pediatric blood cultures tested using BC-GP from January 2014–December 2017.

Table 1
Identification of isolates from positive blood cultures having growth of a single organism by the Luminex Verigene® BC-GP.

Traditional Identification Methods	Number of isolates	Identified to species	Identified to genus	Not Detected
Enterococcus faecalis	88 (6.7%)	85	NA	3
Enterococcus faecium	32 (2.8%)	32	NA	0
Listeria species	1 (<0.5%)	NA	1	0
Streptococcus agalactiae	32 (2.7%)	32	0	0
Staphylococcus aureus	254 (19.4%)	254	0	0
Streptococcus anginosus	12 (1.1%)	12	0	0
Staphylococcus epidermidis	435 (36.3%)	401	14	20
Staphylococcus lugdunensis	6 (0.6%)	6	0	0
Streptococcus pneumoniae	55 (3.9%)	53	2	0
Streptococcus pyogenes	25 (2.0%)	24	0	1
Staphylococcus species	183 (15.0%)	NA	172	11
Streptococcus species	108 (9.5%)	NA	93	15
TOTAL (1231)	1231	899	282	50

BC-GP in all single isolate cultures to the species level. *E. faecalis* and *S. pyogenes* were detected correctly to species level with the exception of 3 *E. faecalis* (out of 88) and 1 *S. pyogenes* (out of 25) which were not detected by BC-GP. All but 7 organisms detected by BC-GP that grew in single isolate cultures were identified as the same organism by Vitek™ MS. These 7 isolates that were correctly identified to the genus level as *Streptococcus* species but incorrectly identified at the species level as *S. pneumoniae* instead of *S. mitis/oralis*. 153 single isolate cultures grew bacterial species not included in the BC-GP panel which were correctly interpreted by the Luminex Verigene® as "Not Detected" (Table 2).

In addition, 112 cultures were found to have multiple different Gram-positive organisms (Table 3). In 77 cultures, BC-GP was able to detect all organisms in the culture correctly that were included as targets on the panel. 1 culture in which BC-GP detected *Staphylococcus* species and *Streptococcus* species was unable to grow *Staphylococcus* species in culture. 3 mixed isolate cultures grew organisms identified by Vitek™ MS as *S. mitis/oralis*. These organisms were falsely identified as *S. pneumoniae* by BC-GP.

3.2. Antimicrobial Resistance Marker Detection

We found excellent overall agreement between BC-GP gene detection and phenotypic susceptibility testing, with only 5 (1%) of samples displaying discordant results (Table 4). Corresponding κ coefficients for *mecA* detection in S. aureus (0.98, 95% CI: 0.96–1), *mecA* detection in *S. epidermidis* (0.93, 95% CI: 0.86–1), and *vanA/B* detection in *E. faecium/faecalis* (1.0, 95% CI: 1–1) suggest near perfect agreement. There were 2 *S. aureus* isolates for which a *mecA* gene was detected by Luminex Verigene®, but were oxacillin susceptible phenotypically.

3.3. Impact on Clinical Care

Evaluation of clinical impact due to discrepant BC-GP results was performed by reviewing a total of 20 patient's charts. The most common misidentification was *S. pneumoniae* by BC-GP that was *S. mitis/oralis* by Vitek™ MS, occurring in 10 cultures. No effect on clinical management was noted in 6, 3 had a possible effect with prolonged antibiotic therapy, and 1 had a definite effect with a lumbar puncture, peripherally inserted central venous catheter placement, and prolonged antibiotic therapy in an infant. BC-GP detected *Streptococcus* species that Vitek™ MS identified as *S. pneumoniae* for 2 patients; neither resulted in clinical effect. In 3 instances, no organism was detected on BC-GP, while a potential pathogen (1 *S. pyogenes*, 2 *S. salivarius*) was identified on culture; no clinical effect was noted for any of the patients. The remaining 4 instances were failure of BC-GP to detect a pathogen in mixed culture (1 missed *E. faecalis*, 2 missed *S. aureus*, 1 missed *S. anginosus*), in which no clinical effect was noted. Lack of clinical effect was most often due to likely continuation of empiric therapy that would have covered the mis/unidentified organism (e.g., for patients with febrile neutropenia).

Table 2
Identification by Vitek™ MS of Gram positive Organisms grown in Monomicrobial blood cultures that were not on the panel for BC-GP.

Organism grown in single isolate blood culture, undetectable by BC-GP	Number of positive blood cultures growing isolate
Abiotrophia/Granulicatella group	2
Actinomyces odontolyticus	2
Aerococcus urinae	1
Anaerobic Gram-positive cocci species	2
Bacillus species	16
Bifidobacterium species	3
Brevibacterium species	3
Brachybacterium	1
Clostridium difficile	1
Clostridium species	6
Corynebacterium species	20
Cutibacterium species *(Propionibacterium)*	16
Dermabacter hominis	1
Enterococcus casseliflavus	1
Enterococcus durans	1
Enterococcus gallinarium	3
Finegoldia magna	4
Gemella haemolysans	2
Gordonia species	1
Granulicatella adiacens	3
Lactobacillus species	6
Leuconostoc species	4
Lysinibacillus species	1
Macrococcus species	1
Microbacterium species	3
Micrococcus species	33
Paenibacillus species	2
Parvimonas micra	1
Peptoniphilus asaccharolyticus	1
Peptostreptococcus species	4
Rothia species	5
Unidentifiable Gram positive bacilli species	2
Unidentifiable Gram positive cocci species0	1
TOTAL	**153**

4. Discussion

For nearly all isolates, Luminex Verigene® BC-GP was as informative as traditional culture identification, and antimicrobial resistance markers were identified at a very high rate of accuracy. Providers can therefore use the identification and antimicrobial resistance marker data gained from Luminex Verigene® with confidence to support antimicrobial selection. For the rare instances where there was disagreement, the clinical impact was minimal, and did not place patients at any increased risk of harm.

In addition to guiding earlier appropriate targeted antimicrobial treatment for bacteremia, in combination with clinical evaluation, Luminex Verigene® BC-GP platform can allow earlier decision-making for discerning positive blood culture isolates likely representing contamination. Of the 878 staphylococcal isolates tested, 618 (70.4%) were either *S epidermidis* or a coagulase-negative staphylococcus that most often is not clinically relevant. Single isolate blood cultures containing the pathogens *S. aureus* and *S. lugdunensis* were identified to the species level, suggesting detection of *Staphylococcus* species at the genus level only will reliably not be a pathogenic strain. In addition, of the 203 isolates not identified by Luminex Verigene® BC-GP, 50 (24.6%) were organisms included on the panel. The remaining 153 would not have been expected to be detected, and most of the organisms were most likely to represent skin contaminants (Table 2). This has the potential to avert unnecessary hospitalizations and antimicrobial exposures associated with increased healthcare costs and adverse risks for patients.

Table 3
Polymicrobial Gram positive isolates from positive blood cultures tested by BC-GP.

Culture Results	Total	BC-GP Match Culture	BC-GP Target Missed (False Negative)	Other BC-GP Targets (False Positive)
>TWO ORGANISMS				
E. faecalis + *E. faecium* + *S. epidermidis*	1	0/1	*S. epidermidis*	
E. faecalis + *S.aureus* + *S. epidermidis*	1	0/1	*S. aureus* + *S. epidermidis*	
S. epidermidis + *Staphylococcus* species (2)	1	1/1		
S. epidermidis + *Streptococcus* species (2)	1	0/1	*S.epidermidis* + *Streptococcus* species (2)	
S. epidermidis + *Streptococcus* species + *Staphylococcus* species	1	0/1	*S. epidermidis*	
Streptococcus species (3) + undetectable by BC-GP	1	1/1		
Streptococcus species (2) + undetectable by BC-GP	1	1/1		
Streptococcus species + *S. epidermidis* + undetectable by BC-GP	1	0/1	*S. epidermidis*	
Streptococcus species (3) + *S. epidermidis*	1	0/1	*S. epidermidis*	*S. pneumoniae*
Streptococcus species (2) + *Staphylococcus* species	1	0/1	*Staphylococcus* species	
S. anginosus + undetectable by BC-GP (2)	1	1/1		
TWO ORGANISMS				
2 undetectable by BC-GP	4	4/4		
E. faecalis + undetectable by BC-GP	4	4/4		
E. faecalis + *Staphylococcus* species	2	0/2	2 *E. faecalis*	
E. faecium + *S. epidermidis*	1	0/1	*S. epidermidis*	
E. faecium + *E. faecalis*	1	0/1	*E. faecalis*	
Staphylococcus species + undetectable by BC-GP	3	2/3	*Staphylococcus* species	
Staphylococcus species (2)	3	3/3		
S. aureus + undetectable by BC-GP	3	2/3	*S. aureus*	
S. aureus + *S. agalactiae*	2	1/2	*S. aureus*	
S. aureus + *E. faecalis*	2	2/2		
S. aureus + *Staphylococcus* species	3	2/3	1 *S. aureus*	
S. aureus + *S. epidermidis*	6	4/6	2 *S. epidermidis*	
S. aureus + Streptococcus species	2	1/2	*S. aureus*	
S. epidermidis + undetectable by BC-GP	5	4/5	*S. epidermidis*	
S. epidermidis + *Staphylococcus* species	26	19/26	6 *S. epidermidis* 1 *Staphylococcus* species	
S. epidermidis + *Streptococcus* species	4	3/4	1 *S. epidermidis*	
S. epidermidis + *S. pyogenes*	1	0/1	*S. epidermidis*	
Streptococcus species + undetectable by BC-GP	6	2/6	3 *Streptococcus* species	S. pneumoniae
Streptococcus species (2)	12	11/12		S. pneumoniae
Streptococcus species + *Staphylococcus* species	8	7/8	5 *Staphylococcus* species 2 *Streptococcus* species	
S. agalactiae + *S. anginosus*	1	0/1	*S. anginosus*	
S. anginosus + undetectable by BC-GP	1	1/1		
S. anginosus + *Streptococcus* species	1	1/1		
TOTAL	112	77/112		

A consistent exception to accurate identification by BC-GP is misidentification of *S. mitis/oralis* as *S. pneumoniae*. This has been reported previously, and the Luminex Verigene® package insert includes false positive results due to cross reaction of *Streptococcus mitis/oralis* and *Streptococcus pneumoniae* due to homologous genetic material as a limitation of the assay (Felsenstein et al., 2016; Luminex Corporation, 2016). Our data further confirms this finding. Of all missed identifications, this had the greatest clinical impact, resulting in longer antibiotic courses and hospital stays for 4 patients, one of whom underwent additional procedures. Providers should consider this known identification exception in practice, but our data suggests little negative clinical impact is likely in this or other misidentification events.

Table 4
Antimicrobial resistance gene markers by Luminex Verigene® BC-GP.

Organism	Resistance Gene	Number of isolates	Number Phenotypic match	Overall Agreement with Phenotype
S. aureus	*mecA* +	95	93	98%
S. aureus	*mecA* -	159	159	100%
S. epidermidis	*mecA* +	139	136	98%
S. epidermidis	*mecA* -	25	25	100%
E. faecium	*vanA/B* +	12	12	100%
E. faecium/faecalis	*vanA/B* -	104	104	100%

In the absence of a predictive marker, waiting until isolate-specific susceptibilities are confirmed is recommended before narrowing to targeted therapy (Leekha et al., 2011). We found BC-GP antimicrobial resistance marker detection to be reliable and predictive of phenotypic results. Isolates in whom *mecA* (*S.* aureus or S. *epidermidis*), or *vanA*, and *vanB* (*E.faecalis* or *E. faecium*) were not detected by BC-GP showed methicillin or vancomycin susceptibility, respectively. Thus, clinical practitioners can use a "not detected" result to guide antibiotic choice confidently. For *mecA* negative isolates, this most likely would result in de-escalation of vancomycin to clinically superior beta-lactam antibiotics and avoiding vancomycin-associated nephrotoxicity. Similarly, *vanA* and *vanB* was present in all phenotypically vancomycin-resistant enterococci (VRE), which could reliably guide the prescriber away from vancomycin and its associated nephrotoxicity. Detection of *mecA* in 5 isolates (2 *S. aureus*, 3 *S. epidermidis*) with phenotypic oxacillin susceptibility was surprising. Why the genetic marker is present but not

phenotypically expressed, such as due a defect in the *mecA* gene itself or lack of gene expression is possible, and the subject of future study.

A small percentage of positive pediatric blood cultures containing Gram-positive organisms can be expected to be polymicrobial. One center described that 7.6% (95/1252) of patient blood cultures to contain multiple Gram-positive isolates, similar to the 7.5% (112/1503) mixed cultures experienced in our study (Leuangarun and Leelarasamee, 2012). Understanding the clinical implications of BC-GP performance on polymicrobial cultures is made challenging by the low incidence and high variety of combinations. For the majority of cohort patients, the multiple organisms represented were most likely multiple contaminants (Table 3). BC-GP performance on a polymicrobial culture would therefore be expected to have little effect on therapeutic management. In some instances, especially when multiple pathogens were identified on culture, relying on BC-GP data alone may not have led to optimized therapy. Nonetheless, no clinical impact was identified in cohort patients with clinically significant multi-organism bloodstream infections.

Collaboration between the Clinical Laboratory and Antimicrobial Stewardship Program with use of local antibiograms data, organism identification, and in particular detection of antimicrobial resistance gene markers can decrease time to adequate antimicrobial therapy and improve patient outcomes, which was previously not possible by traditional culture and antimicrobial susceptibility testing (Caliendo et al., 2013; Kumar et al., 2009; Leuangarun and Leelarasamee, 2012; Marquet et al., 2015). Clinicians can be confident the information they gain from Luminex Verigene® BC-GP. Both positive and negative findings can predict culture and susceptibility results and allow earlier decision making in patient care. The few exceptions where the molecular and culture methods did not agree all favored the more conservative clinical approach, and did not increase risk of patient harm. Ongoing studies are being pursued to examine the contribution of this technology to improved clinical outcomes, decreased healthcare costs, and prevention of unnecessary harm among bacteremic pediatric patients.

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