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Evaluation of the Verigene Gram-Positive Blood Culture Nucleic Acid Test for Rapid Detection of Bacteria and Resistance Determinants

Christina M. Wojewoda,[a] Linda Sercia,[b] Maria Navas,[b] Marion Tuohy,[b] Deborah Wilson,[b] Geraldine S. Hall,[b] Gary W. Procop,[b] Sandra S. Richter[b]

Department of Pathology, Fletcher Allen Health Care/University of Vermont, Burlington, Vermont, USA[a]; Department of Clinical Pathology, Cleveland Clinic, Cleveland, Ohio, USA[b]

Rapid identification of pathogens from blood cultures can decrease lengths of stay and improve patient outcomes. We evaluated the accuracy of the Verigene Gram-positive blood culture (BC-GP) nucleic acid test for investigational use only (Nanosphere, Inc., Northbrook, IL) for the identification of Gram-positive bacteria from blood cultures. The detection of resistance genes (*mecA* in *Staphylococcus aureus* and *Staphylococcus epidermidis* and *vanA* or *vanB* in *Enterococcus faecium* and *Enterococcus faecalis*) by the BC-GP assay also was assessed. A total of 186 positive blood cultures (in BacT/Alert FA bottles) with Gram-positive cocci observed with Gram staining were analyzed using the BC-GP assay. The BC-GP results were compared with the identification and susceptibility profiles obtained with routine methods in the clinical laboratory. Discordant results were arbitrated with additional biochemical, cefoxitin disk, and repeat BC-GP testing. The initial BC-GP organism identification was concordant with routine method results for 94.6% of the blood cultures. Only 40% of the *Streptococcus pneumoniae* identifications were correct. The detection of the *mecA* gene for 69 blood cultures with only *S. aureus* or *S. epidermidis* was concordant with susceptibility testing results. For 3 of 6 cultures with multiple *Staphylococcus* spp., *mecA* detection was reported but was correlated with oxacillin resistance in a species other than *S. aureus* or *S. epidermidis*. The detection of *vanA* agreed with susceptibility testing results for 45 of 46 cultures with *E. faecalis* or *E. faecium*. Comparison of the mean times to results for each organism group showed that BC-GP results were available 31 to 42 h earlier than phenotypic identifications and 41 to 50 h earlier than susceptibility results.

Bloodstream infections are one of the leading causes of death in the United States (1). Sepsis is fatal in 20 to 50% of cases (2) and is associated with prolonged hospitalization, with higher health care costs (3). The clinical microbiology laboratory plays a vital role in the treatment of patients with bloodstream infections. While current methods for the detection and characterization of bloodstream pathogens can take days, the risk of death from sepsis increases by 6 to 10% per hour from the onset of shock to the start of effective antimicrobial treatment (4).

Over 50% of organisms identified in positive blood cultures are Gram-positive bacteria (5). Gram-positive organisms also are common contaminants of blood cultures. Therefore, rapid differentiation of pathogens from contaminants would be clinically useful.

The Verigene Gram-positive blood culture (BC-GP) nucleic acid test for investigational use only (IUO) (Nanosphere, Northbrook, IL) is a random-access, automated test that performs nucleic acid extraction directly from positive blood culture media, hybridization onto a microarray, and analysis in 2.5 h. Targets in the assay include *Staphylococcus* spp., *Streptococcus* spp., *Micrococcus* spp., *Listeria* spp., *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus lugdunensis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, *Enterococcus faecalis*, and *Enterococcus faecium*. In addition, if *S. aureus* or *S. epidermidis* is detected, then the presence or absence of the *mecA* gene is reported. Similarly, if *E. faecium* or *E. faecalis* is detected, then the presence or absence of the *vanA* and *vanB* genes is reported. The BC-GP test was approved by the U.S. Food and Drug Administration (FDA) on 27 June 2012 for the reporting of all IUO targets except *Micrococcus* spp. (6).

We evaluated the performance of the Verigene BC-GP IUO assay in comparison with routine laboratory methods used in the clinical laboratory. A recent evaluation of the BC-GP assay (7) tested blood cultures from a blood culture system (VersaTREK; Trek Diagnostic Systems, Cleveland, OH) that is used by <10% of U.S. laboratories, while our study utilized the BacT/Alert instrument (bioMérieux, Durham, NC), which is found in ~50% of laboratories (N. Safwat, personal communication). Another novel aspect of our study is the assessment of the time from Gram stain result reporting to identification and susceptibility result reporting for current laboratory methods, in comparison to the time for BC-GP results. This research was conducted at the Cleveland Clinic, after approval by the institutional internal review board.

(This study was presented in part at ID Week, San Diego, CA, 20 October 2012.)

MATERIALS AND METHODS

Blood culture samples. The BC-GP IUO test was evaluated with blood cultures submitted for testing at the Cleveland Clinic microbiology laboratory in February to August 2012. Positive aerobic blood culture samples (in BacT/Alert FA bottles [bioMérieux, Durham, NC]) that contained Gram-positive cocci from unique patients were included in the study. Specimens were excluded if multiple morphologies were observed on Gram stains. Coagulase-negative staphylococci (CoNS), as determined by peptide nucleic acid-based fluorescence *in situ* hybridization (PNA-FISH)

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Address correspondence to Sandra S. Richter, richtes@ccf.org.
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TABLE 1 Comparison of Verigene BC-GP results and standard laboratory method results for 174 blood cultures yielding one organism[a]

Verigene BC-GP result	No. (actual/expected) of blood cultures with Verigene results	No. (%) of Verigene results concordant with standard laboratory method results		Sensitivity (%)[b]	Specificity (%)[b]
		Initial assay	Repeat assay		
Staphylococcus aureus	44/44	44 (100)	NR[c]	100	100
Staphylococcus epidermidis	25/25	25 (100)	NR	100	100
Staphylococcus lugdunensis	1/1	1 (100)	NR	100	100
Staphylococcus spp.[d]	25/25	25 (100)	NR	100	100
Micrococcus spp.	1/2	1 (50)[e]	1 (50)[e]	50	100
Streptococcus pneumoniae	5/2	2 (40)[f]	2 (40)[f]	100	98.2
Streptococcus anginosus group	4/4	4 (100)	NR	100	100
Streptococcus agalactiae	6/6	6 (100)	NR	100	100
Streptococcus pyogenes	1/1	1 (100)	NR	100	100
Streptococcus spp.[g]	13/17	13 (76.5)[g]	13 (76.5)[g]	76.5	100
Enterococcus faecalis	13/13	13 (100)	NR	100	100
Enterococcus faecium	27/29	27 (93.1)[h]	29 (100)[h]	93.1	100
Nothing detected	9/5[i]	5 (55)[e,g,h]	5 (71)[j]	100	97.6
mecA	44/44	44 (100)	NR	100	100
vanA	23/24	23 (95.8)	24 (100)[h]	95.8	100

[a] BC-GP, Gram-positive blood culture.
[b] Sensitivity and specificity values were based on the initial Verigene BC-GP results.
[c] NR, no repeat of the Verigene assay was required for this organism group.
[d] The Verigene results were *Staphylococcus* spp. for 25 isolates identified by the laboratory as coagulase-negative staphylococci ($n = 17$), *Staphylococcus hominis* ($n = 5$), *Staphylococcus capitis* ($n = 2$), and *Staphylococcus haemolyticus* ($n = 1$). The results do not include those for *Staphylococcus* spp. in conjunction with *S. aureus*, *S. epidermidis*, or *S. lugdunensis*.
[e] The Verigene result was "nothing detected" for 1 of the 2 blood cultures with *Micrococcus* spp.
[f] Three of the 5 blood cultures with Verigene results of *S. pneumoniae* grew isolates identified as *S. mitis* group by Vitek 2 and biochemical testing (optochin resistant and bile solubility negative).
[g] The Verigene result was "nothing detected" for one blood culture isolate identified by the laboratory as viridans group streptococci. The 13 isolates with Verigene results of *Streptococcus* spp. were identified by the laboratory as *S. bovis* group ($n = 4$), *S. mitis* group ($n = 2$), *S. salivarius* group ($n = 1$), *S. salivarius/S. mitis* group ($n = 1$), viridans group streptococci ($n = 4$), and *Streptococcus* spp. ($n = 1$). The results do not include those for *Streptococcus* spp. in conjunction with *S. pneumoniae*, *S. anginosus* group, *S. agalactiae*, or *S. pyogenes*.
[h] The Verigene results were incorrect as nothing detected in initial testing for two blood cultures; repeat testing indicated *E. faecium* (*vanA* positive in one case).
[i] One *Enterococcus* species (not *E. faecium* or *E. faecalis* by Vitek 2) was correctly reported as nothing detected. Four additional isolates without targets in the BC-GP assay (identified by the laboratory as *Abiotrophia* spp., nutritionally variant streptococci, *Dolosigranulum* or *Facklamia* spp., and diphtheroid) were correctly reported as nothing detected.
[j] Repeat test results were correctly changed to *E. faecium* for 2 cultures. The other 2 cultures (*Micrococcus* spp. and *Streptococcus* spp.) with targets in the BC-GP assay were not detected.

(AdvanDx, Woburn, MA), were limited according to a research protocol to increase the variety of organisms included in the study. Aliquots of 2 ml were aseptically removed from the blood culture bottles. If a sample could not be run within 12 h, then it was refrigerated at 2 to 8°C for up to 48 h. The samples were frozen at −70°C if they could not be run until >48 h after becoming positive.

BC-GP IUO assay. The BC-GP assay was performed according to the manufacturer's package insert. For each test, an extraction tray, test cartridge, and utility tray were inserted into the Verigene Processor *SP*. A 350-μl aliquot of blood culture broth was added to the sample well. After 2.5 h, the test cartridge was removed from the Verigene Processor *SP* and the reagent pack was separated from the substrate holder. The substrate holder was allowed to dry and then was inserted into the Verigene Reader for analysis.

Data analysis. Each BC-GP organism identification was compared with results obtained in the clinical laboratory with routine methods that included PNA-FISH, Vitek 2 (bioMérieux, Durham, NC), and biochemical (catalase, slide coagulase, pyrrolidonyl arylamidase [PYR], bile solubility, and optochin susceptibility) analyses (8). Discordant identification results were arbitrated with a repeat BC-GP assay and additional biochemical testing. BC-GP detection of resistant determinants was compared with susceptibility results from a Vitek 2 GP70 card. For isolates of CoNS without Vitek 2 susceptibility results, cefoxitin disk diffusion testing was performed (9). BC-GP detection of *mecA* was considered concordant if the isolate was resistant to cefoxitin or oxacillin, and BC-GP detection of *vanA* or *vanB* in enterococci was considered concordant if the isolate was resistant to vancomycin. Discordant resistance determinant results were arbitrated with a repeat BC-GP assay and disk diffusion testing (9).

Time-to-result analysis. For current methods, the times from Gram stain result reporting to PNA-FISH result (*S. aureus*), laboratory identification (all other organisms), and susceptibility result (*S. aureus*, *S. epidermidis*, *E. faecalis*, and *E. faecium*) reporting were calculated. For the Verigene, the time from Gram stain result reporting to BC-GP result reporting was determined only for samples that were analyzed within 12 h after the positive blood culture signal.

RESULTS

There were 186 blood cultures meeting the criteria for inclusion in the study. Subculture to solid medium yielded one isolate for 174 of those samples. Two or more isolates were recovered from 12 blood culture broths. The BC-GP organism identification agreed with the results of routine laboratory methods for 94.6% of the 186 blood cultures. Three of the 10 cultures with discordant organism identification results were among the 12 blood cultures that yielded multiple isolates (i.e., polymicrobial).

For the 174 blood cultures that contained only one organism, 167 identification results (96.0%) were initially concordant (Table 1). Three of the blood cultures with a BC-GP result of *S. pneumoniae* grew isolates identified as *Streptococcus mitis* group by the

TABLE 2 Comparison of Verigene results and standard laboratory method results for 12 cultures yielding multiple organisms

Verigene BC-GP result	As expected?	Expected Verigene result	Culture result
E. faecalis	No[a]	*E. faecalis*, *Staphylococcus* spp.[a]	*E. faecalis*, *Staphylococcus simulans*, *Staphylococcus sciuri*[a]
E. faecium, *vanA*	No[a]	*E. faecium*, *vanA*, *Staphylococcus* spp.[a]	*E. faecium* (vancomycin resistant), *Staphylococcus lentus*[a]
Staphylococcus spp., *S. aureus*, *mecA*[b]	No[b]	*Staphylococcus* spp., *S. aureus*	*S. aureus* (oxacillin susceptible), *Staphylococcus hominis* (oxacillin resistant)[b]
Staphylococcus spp., *S. epidermidis*, *mecA*[c]	No[c]	*Staphylococcus* spp., *S. epidermidis*	*S. epidermidis* (oxacillin susceptible), *S. hominis* (oxacillin resistant)[c]
Staphylococcus spp., *S. epidermidis*, *mecA*[d]	No[d]	*Staphylococcus* spp.	*S. hominis* (oxacillin resistant), *Staphylococcus cohnii* (oxacillin resistant), *Globicatella sanguinis*
E. faecalis	Yes		*E. faecalis*, *Enterobacter aerogenes*
Staphylococcus spp., *S. aureus*, *mecA*	Yes		*S. aureus* (oxacillin resistant), coagulase-negative staphylococci[e]
Staphylococcus spp., *S. aureus*, *Streptococcus* spp.	Yes		*S. aureus* (oxacillin susceptible), group G streptococci
Staphylococcus spp., *S. aureus*, *S. epidermidis*, *mecA*[f]	Yes		*S. aureus* (oxacillin susceptible), *S. epidermidis* (oxacillin resistant)
Staphylococcus spp., *S. epidermidis*, *mecA*, *E. faecalis*, *vanA*	Yes		Coagulase-negative staphylococci (oxacillin resistant), *E. faecalis* (vancomycin resistant)
Streptococcus spp., *Streptococcus anginosus* group	Yes		*S. anginosus* group, diphtheroid
Streptococcus spp.	Yes		*S. mitis/oralis*, *Rothia mucilaginosa*

[a] Reported by the laboratory as coagulase-negative staphylococci and by Verigene as not detected; susceptibility testing was not performed.
[b] The result would be interpreted as MRSA because *S. epidermidis* is the only coagulase-negative staphylococcal species for which a *mecA* Verigene result is expected.
[c] *S. epidermidis* is the only coagulase-negative staphylococcal species for which a *mecA* result is expected.
[d] Although both species of coagulase-negative staphylococci were resistant to oxacillin, neither was *S. epidermidis*.
[e] The species was not determined and susceptibility testing was not performed.
[f] The Verigene result does not indicate whether *mecA* is in *S. aureus* or *S. epidermidis*.

Vitek 2 and biochemical testing (optochin resistant and bile solubility negative). The BC-GP assay failed to detect *E. faecium* initially in two cultures, but these organisms were detected in the repeat tests. Of the other two blood cultures, with incorrect "not detected" results for all targets (in initial and repeat testing), one grew *Micrococcus* sp. and one grew viridans group streptococci. The sensitivity and specificity for the detection of *mecA* were 100% for the 69 blood cultures containing *S. aureus* or *S. epidermidis*. One of the two *E. faecium* isolates that was missed initially was vancomycin resistant, with *vanA* gene detection being reported with the identification on repeat BC-GP testing.

Although a single morphology was reported from the Gram staining for all blood cultures enrolled in the study, two or three organisms were recovered in the subcultures from 12 bottles (Table 2). Nine of these 12 cultures had BC-GP organism identifications that were concordant with the results of routine laboratory methods. Coagulase-negative staphylococci (*Staphylococcus simulans* plus *Staphylococcus sciuri* or *Staphylococcus lentus*) were not detected by BC-GP testing in 2 blood cultures with enterococci (*E. faecalis* and *E. faecium*, respectively). For a third blood culture, *S. epidermidis* was reported initially but different species (*Staphylococcus hominis* and *Staphylococcus cohnii*) grew from the culture. Repeat BC-GP testing was concordant with a result of *Staphylococcus* spp. (Table 3).

Discordant *mecA* results occurred for three blood cultures with multiple organisms. BC-GP testing reported the presence of the *mecA* gene in 3 samples, in conjunction with *S. aureus* or *S. epidermidis*. In each culture, however, the isolates for which a *mecA*-positive result would be expected were actually oxacillin susceptible and the *mecA* gene was correlated with oxacillin resistance in a different *Staphylococcus* sp.

The shortest mean time from the Gram stain report to organism identification was 4.7 h (PNA-FISH result) for *S. aureus*, and the longest time was 45.5 h for *Enterococcus* spp. (Table 4). The mean times from the Gram stain report to susceptibility results were 43.3 h for *S. aureus*, 51 h for *S. epidermidis*, and 53.8 h for *Enterococcus* spp. The BC-GP assay can be performed in 2.5 h, but samples were batched for this study. For blood cultures that were tested without being refrigerated or frozen, the shortest mean BC-GP result time was for *S. aureus* (2.6 h from the time of the Gram stain report) and the longest was for *S. epidermidis* (4.1 h). Using mean values, the BC-GP results were available 30.5 to 41.7 h earlier than phenotypic identifications and 40.7 to 50 h earlier than susceptibility results.

DISCUSSION

Rapid identification and resistance detection for positive blood cultures should be the goal of every laboratory. Although some biochemical identification and susceptibility testing results were available less than 24 h after the Gram stain report in the current study, the mean times were much greater (Table 4). The Verigene BC-GP assay has a turnaround time of 2.5 h, with 5 min of hands-on time, while the turnaround time for the standard PNA-FISH method used in this study is 1.5 h, with 30 min of hands-on time. The longer turnaround times for both assays observed in this study are due to samples being batch tested for workflow ease. The BC-GP assay was not integrated into the normal workflow of the clinical laboratory; instead, it was performed in a research laboratory that was physically separate. The ease of use for the BC-GP test is conducive to on-demand testing, which would decrease the times to identification and resistance results even further than shown in our study with batch testing.

TABLE 3 Comparison of initial Verigene BC-GP results and standard laboratory method results for 12 blood cultures yielding multiple organisms[a]

Verigene BC-GP result	No. (actual/expected) of blood cultures with Verigene results	No. (%) of Verigene results concordant with standard laboratory method results		Sensitivity (%)[b]	Specificity (%)[b]
		Initial assay	Repeat assay		
Staphylococcus aureus	4/4	4 (100)	NR[c]	100	100
Staphylococcus epidermidis	4/3	4 (75)	3 (100)	100	88.9
Staphylococcus spp.	1/3	1 (33.3)	1 (33.3)	33.3	100
Streptococcus anginosus group	1/1	1 (100)	NR	100	100
Streptococcus spp.	2/2	2 (100)	NR	100	100
Enterococcus faecalis	3/3	3 (100)	NR	100	100
Enterococcus faecium	1/1	1 (100)	NR	100	100
mecA	6/3	6 (50)	5 (60)	100	66.7
vanA	2/2	2 (100)	NR	100	100

[a] BC-GP, Gram-positive blood culture.
[b] Sensitivity and specificity values were based on the initial Verigene results.
[c] NR, no repeat of the Verigene assay was required for this organism group.

The cost savings with rapid organism identification and resistance gene detection for positive blood cultures that were reported for other testing methodologies should apply also to the BC-GP and offset the retail price of $80 per test (M. McGarrity, personal communication). Ly et al. demonstrated that PNA-FISH differentiation of *Staphylococcus* spp. and early notification were associated with lower mortality rates and less antimicrobial use ($P = 0.01$), with a trend of lower hospital charges ($19,441; $P = 0.09$) (10). Rapid detection of methicillin-resistant *S. aureus* (MRSA) bacteremia using the GeneXpert system (Cepheid) was associated with a reduction in mean hospital costs of approximately $21,000 (11). After implementation of a *mecA* PCR assay, Nguyen et al. demonstrated decreased vancomycin usage and shortened hospital lengths of stay (12).

For pure cultures, the BC-GP assay performed well, compared with routine laboratory methods. Due to the genetic similarity of *Streptococcus mitis* and *S. pneumoniae* (13), it is not surprising that the assay reported *S. pneumoniae* for three *S. mitis* group isolates. Since only 40% of the BC-GP *S. pneumoniae* results (2/5 cases) were correct, a preliminary report of "*Streptococcus* species (*S. pneumoniae* or *S. mitis* group; confirmation to follow)" would be prudent. The lack of BC-GP detection of *E. faecium* in the initial testing of two single-organism blood cultures probably reflects low organism loads. If laboratories do not report "not detected" results for all targets, then incorrect therapeutic changes for blood cultures with low organism loads might be avoided.

Only one of the two blood cultures with *Micrococcus* spp. included in the study was identified by BC-GP. The infrequent recovery of *Micrococcus* spp. and limited clinical trial data likely explain its exclusion from the BC-GP *in vitro* diagnostic (IVD) test.

Evaluations of the BC-GP using other blood culture systems demonstrated predominantly *Staphylococcus* spp. and fewer enterococci. A study assessing the BC-GP in conjunction with the Bactec system (BD Diagnostics, Sparks, MD) found correct detection of *Staphylococcus* spp. but lower concordance rates for viridans group streptococci and enterococci (14). An evaluation of BC-GP testing with VersaTREK blood culture bottles reported 98% and 95% concordance for detection of *S. aureus* and enterococci, respectively (7). The VersaTREK study reported only one *S. mitis* group isolate misidentified by the BC-GP as *S. pneumoniae* (7), while this occurred with 3 blood cultures in our study performed with BacT/Alert bottles. There was a predominance of CoNS ($n = 117$) with fewer *Enterococcus* spp. ($n = 19$) in the VersaTREK study, but a similar problem with enterococcal detection was noted (1 of 15 *E. faecalis* isolates was undetected) (7).

Although there was an attempt to exclude mixed cultures based on the Gram stain results in the current study, 12 samples contained multiple organisms. The percentage of concordant organism identifications was lower for cultures with multiple organisms (75%) than for cultures with single organisms (96.0%). A lower concordance rate also was reported for the 25 polymicrobial cultures included in the VersaTREK study (7).

True polymicrobial sepsis is uncommon, occurring in only 4.7% of episodes in one series (5). The recovery of multiple organisms in a blood culture often is the result of a contaminant along with a pathogen. In the current study, the BC-GP assay was unable to detect CoNS in two cultures when they were mixed with entero-

TABLE 4 Times to results for the Verigene BC-GP assay in comparison with other methods

Organism	Mean (range) time (h) from Gram stain reporting to routine method results			
	BC-GP[a]	PNA-FISH[a]	Biochemical identification[b]	Susceptibility testing
S. aureus	2.6 (2.5–3)	4.7 (1.5–14)		43.3 (19.5–74.5)
S. epidermidis	4.1 (2.5–13)	5.2 (1.5–14)	38.6 (18.5–72)	51 (40–72)
Enterococcus spp.	3.8 (2.5–5)		45.5 (16–106)	53.8 (16–111)
Coagulase-negative staphylococci	3.3 (2.5–4.5)	4.76 (2.5–8)	33.8 (16–147)	
Streptococcus spp.	3.4 (2.5–4.5)		42 (17.5–76.5)	

[a] The times to results for BC-GP and PNA-FISH were influenced by the testing of specimens in batches.
[b] Identification using Vitek 2 or reference biochemical methods.

cocci. The clinical impact of not detecting the CoNS in these particular cases would be minimal, since they were classified as probable contaminants by the laboratory. The lower sensitivity might reflect lower numbers of CoNS, relative to the true pathogen.

The BC-GP algorithm allowing *mecA* results only for *S. aureus* and *S. epidermidis* makes interpretation of mixed cultures difficult (7, 15). In this study, two mixed blood cultures with *mecA*-positive results contained oxacillin-susceptible *S. aureus* or *S. epidermidis* and the *mecA* gene was correlated with oxacillin resistance in a different *Staphylococcus* sp. (Table 2). The therapeutic consequence would be unnecessary vancomycin use for an isolate presumed to be MRSA that was actually susceptible to methicillin. The more serious discordance would be failure to detect *mecA*, leading to inappropriate de-escalation of therapy. A third mixed blood culture had an incorrect result of *S. epidermidis* with *mecA*, but the culture contained two other species of oxacillin-resistant CoNS; repeat testing was concordant with a result of *Staphylococcus* spp. It will be important for laboratories to clarify reporting to ensure that clinicians realize that *mecA* detection occurs for only one species of CoNS (*S. epidermidis*). Future FDA approval for the reporting of *mecA* status for CoNS other than *S. epidermidis* would improve the utility of the BC-GP assay.

In conclusion, the Verigene BC-GP assay provided acceptably accurate organism identification and detection of resistance genes, compared with routine laboratory methods, with better performance in pure cultures. A result of "not detected" for all targets was incorrect 44% of the time, and 40% of isolates with BC-GP *S. pneumoniae* results were identified as *S. mitis* group by the laboratory. The *mecA* gene results were difficult to interpret in mixed cultures with multiple *Staphylococcus* spp. The organisms not correctly detected in polymicrobial blood cultures were CoNS. The availability of BC-GP results 31 to 42 h earlier than the results of routine biochemical identification methods and 41 to 50 h earlier than susceptibility results should promote antimicrobial stewardship and improve clinical outcomes.

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