Impact of a Rapid Blood Culture Assay for Gram-Positive Identification and Detection of Resistance Markers in a Pediatric Hospital

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- Context.—Molecular diagnostics allow for rapid identification and detection of resistance markers of bloodstream infection, with a potential for accelerated antimicrobial optimization and improved patient outcomes. Although the impact of rapid diagnosis has been reported, studies in pediatric patients are scarce.

- Objective.—To determine the impact of a molecular blood-culture assay that identifies a broad-spectrum of pathogens and resistance markers in pediatric patients with gram-positive bloodstream infections.

- Design.—Data on the time to antimicrobial optimization, the length of hospitalization, and the hospital cost following implementation of a rapid assay were prospectively collected and compared with corresponding preimplementation data.

- Results.—There were 440 episodes from 383 patients included, 221 preimplementation episodes and 219 postimplementation episodes. Overall time to antimicrobial optimization was shortened by 12.5 hours ($P = .006$), 11.9 hours ($P = .005$) for bloodstream infections of *Staphylococcus aureus* specifically. Duration of antibiotics for those with probable blood-culture contamination with coagulase-negative staphylococci was reduced by 36.9 hours ($P < .001$). Median length of stay for patients admitted to general pediatric units was 1.5 days shorter ($P = .04$), and median hospital cost was $3757 ($P = .03$) less after implementation. For *S aureus* bloodstream infections, median length of stay and hospital cost were decreased by 5.6 days ($P = .01$) and $13 341 ($P = .03$), respectively.

- Conclusions.—Implementation of molecular assay for the detection of gram-positive pathogens and resistance markers significantly reduced time to identification and resistance detection, resulting in accelerated optimization of therapy, shorter length of stay, and decreased health care cost.


Bloodstream infections (BSIs) are associated with significant health care cost and prolonged hospital stays. Rapid initiation of effective antimicrobial treatment is a mainstay of therapy because delay is associated with increased morbidity and mortality. The workup of pathogens in the microbiology laboratory is a key, contributing factor that directly affects patient survival. Novel methods that allow for rapid identification of pathogens, with the ability to detect resistance markers, are, therefore, promising tools to significantly affect overall patient care.

Recent studies in adults have demonstrated the clinical and economic effect of laboratory interventions using molecular methods. Gram-positive organisms are implicated in more than 50% of all bacterial BSIs, and rapid identification directly correlates with improved patient outcomes, decreased hospital lengths of stay (LOSs), and decreased hospital costs. Detection of the mecA gene in methillin-resistant *Staphylococcus aureus* has been demonstrated to be an effective tool for directing vancomycin usage as well as reducing both hospital LOSs and costs. In addition, a recent study showed that the Verigene gram-positive blood culture (BC-GP, Nanosphere Inc., Northbrook, Illinois) assay had a positive impact in patients with enterococcal BSIs. However, outcome data for such interventions in pediatric patients is scarce.

We sought to assess the effect of integrating the BC-GP assay for the identification of 12 common gram-positive organisms and 3 resistance determinants on (1) antimicrobial optimization, (2) patient outcomes, and (3) health care cost in a large, tertiary, pediatric hospital. We prospectively compared patients presenting with BSIs before and after
BC-GP assay implementation and hypothesized that the BC-GP assay would allow for better care of patients with gram-positive BSIs.

**METHODS**

**Study Design**

This single-center study of the BC-GP assay was conducted at Children’s Hospital Los Angeles (California). The study protocol was reviewed and approved by the institutional review board and ethics committee at that hospital.

Blood culture samples from pediatric patients, aged 1 day to 21 years, who presented with a blood culture positive for a gram-positive bacteria targeted by the BC-GP assay were included. The microbiology laboratory operates and offers all tests 24 h/d, 7 d/wk. Input from the infectious disease team was dependent on consultation request. Institutional policy mandates a consultation for all BSIs caused by *S. aureus*.

**Preintervention Study Period (October 2011 to January 2013)**

All blood culture specimens were obtained and processed using the BacT/ALERT (bioMérieux, Durham, North Carolina) automated blood culture system. Gram stains were processed, electronically reported in the hospital electronic information system, and microbiology laboratory staff initiated phone communication to the treating physician within 10 minutes of blood culture positivity. Positive blood cultures were inoculated onto culture media, and organism identification was carried out using conventional methods, including Vitek II (bioMérieux) and other biochemical tests. Routine susceptibility testing for *S. aureus*, *Enterococcus faecium*, and *Enterococcus faecalis* was performed using Vitek II and/or Etest (bioMérieux). Screening for methicillin resistance in staphylococci was performed using cefoxitin screening by disk diffusion. Final identification and susceptibility results were reported electronically without additional active physician notification. For coagulase-negative staphylococci (CoNS) considered probable contaminants, no further identification and susceptibility testing was performed unless per physician request.

**Postintervention Study Period (February 2013 to February 2014)**

Positive blood cultures were handled in the same manner as the preintervention study period, with the addition of the BC-GP assay. All positive bottles are still inoculated onto culture media to rule-out cases of polymicrobial infections, for further identification to species level (when the BC-GP assay only identified organisms to genus level), and for routine susceptibility testing, when appropriate. The assay was implemented as a routine diagnostic test in February 2013 and demonstrated a concordance rate of 95.8% in our institution. The BC-GP assay identifies 12 gram-positive targets, including *S. aureus*, *E. faecium*, and *E. faecalis*, and 3 resistance determinants (mecA, vanA, vanB) directly from positive blood cultures. The BC-GP assay was performed within 4 hours of blood cultures positive for gram-positive cocci. Presence or absence of mecA and vanA/vanB genes was confirmed by routine susceptibility testing. In addition to telephone notification of Gram stain results, microbiology laboratory staff also called physicians with the BC-GP result within 4 hours of the Gram stain result. The presence or absence of mecA was reported as either presumptive methicillin-resistant *S. aureus* or methicillin-susceptible *S. aureus*. Similarly, reporting of presumptive vancomycin-resistant enterococci or vancomycin-susceptible enterococci was determined by presence or absence of vanA/B gene.

**Data Collection**

In the preimplementation period, patients were identified through the laboratory information system. In the postimplementation period, all positive blood cultures tested by the BC-GP assay were included. All patients presenting with a positive blood culture for an organism targeted by the BC-GP assay during the study periods were included. Clinical data collected from medical records included demographic information, comorbidities, primary care team and unit the patient was admitted to, and pathogens or pathogens and bacterial susceptibilities as identified by conventional methods and by the BC-GP assay. Only the first positive blood culture was included in the analysis in patients with repeat positives within the same infectious episode. Positive blood cultures that were collected more than a minimum of 14 days apart were considered new infectious episodes and included in the microbiologic diagnostics and antimicrobial optimization data analysis.

Appropriate antimicrobial therapy was defined as a regimen that included at least one agent to which the pathogen demonstrated in vitro susceptibility, or decreasing the number of antimicrobials used in combination when fewer agents were sufficient. For example, continued therapy directed against gram-negative rods in a confirmed case of gram-positive BSI, without additional laboratory or clinical indication, would be considered unnecessary. Antimicrobial therapy was defined as optimized when appropriate antimicrobials were initiated; when de-escalation of therapy was based on identification results, susceptibility results, or resistance detection; when therapy was broadened based on laboratory results, patient’s clinical status, or institutional antibiogram; and when antimicrobials were discontinued in cases of blood culture contamination with CoNS. *Probable contaminant* was defined as a single, positive blood-culture bottle with CoNS drawn from a peripheral site or with a central venous access device (CVAD). In addition, clinical assessment was performed to determine whether or not a case should be treated as a true BSI, particularly when CVAD was involved or in patients with significant comorbidities.

Polymicrobial infections were also included in the assessment, and the specific pathogens were factored in when determining appropriate antimicrobial management. A pediatric infectious diseases physician and a pharmacist assessed time to antimicrobial optimization, de-escalation, and discontinuation and the clinical appropriateness of therapy independent of the BC-GP result. Agreement was high, and discrepant assessments were resolved by involving another pediatric infectious diseases physician as a third assessor.

**Outcomes**

Durations between time points were calculated as specified in the “Results” section. Patients who were transferred to another facility or presented to an outpatient facility (eg, emergency department, infusion center, dialysis unit) without subsequent hospitalization were excluded from LOS and cost analysis. The LOS and cost analysis were calculated in 2 ways: based on patient admission to all hospital units and based on patients admitted to only general pediatric units. The LOS and hospital costs were compared between preimplementation and postimplementation groups. Total LOS from admission to discharge and LOS from onset of BSI (date of blood culture collection) to discharge were calculated.

Severity of illness during the hospitalization and case mix index were assigned by the Health Information Department and were based on the documentation present in the patient chart after discharge. Data relating to cost, severity of illness, case mix index, and LOS were provided by the Financial Support Services at Children’s Hospital Los Angeles, blinded to the assigned inter-
vention group and the type and time of the intervention. Overall hospital costs were calculated based on all direct costs incurred within all services during hospitalization, including room and board, medications, consult services, radiology, and laboratory. All documentation and calculation of length of stay, cost, severity, and case mix index were consistent throughout the entire study period.

Statistical Analysis
Quantitative variables were reported as absolute numbers and percentages and expressed by means and standard deviations if normally distributed and by median and interquartile range (IQR) if not. Demographic data pertaining to patient characteristics were analyzed by patient numbers, and information on microbiologic diagnosis and antimicrobial management were analyzed by the number of BSI episodes that occurred during the study period. Comparisons of continuous variables between groups to test for equality were performed using the *t* test, when appropriate, or the Mann-Whitney test when data were highly skewed. Tests of association between categoric variables were based on \( \chi^2 \) and Fisher exact tests. To investigate time trends in mean time to optimization, segmented (piecewise) linear-regression analysis was used, which allowed for a change in both the regression slope and the intercept value after introduction of the BC-GP assay. All \( p \) values reported are 2-sided and were considered statistically significant if less than .05. Statistical computations were performed using SPSS 22.0 (SPSS Inc, Chicago, Illinois).

RESULTS
Patient Cohort
Two hundred twenty-one blood cultures from 194 patients in the preimplementation group and 219 blood cultures from 189 patients in the postimplementation period met study criteria and were included (Figure 1). Patient demographics, comorbidities, and sample origin were compared between the two groups and are summarized in Table 1. Median age was 18.2 months in the preimplementation group and 20.6 months in the postimplementation group \((p = .91)\). Most patients had significant comorbidities, particularly gastrointestinal disorders, resulting in dependence on total parenteral nutrition, prematurity, and hematologic malignancies (Table 1). Of 221 BSI episodes, 140 (63.3%) and 139 of 219 BSI episodes (63.5%) had CVADs in the preimplementation and postimplementation groups, respectively. Fifty percent (220 of 440) of blood cultures originated from CVADs (Table 1).

There were 184 hospitalizations in each group; 87 (47.2%) and 94 (51.1%) admissions were to the general pediatric unit for preimplementation and postimplementation groups, respectively. The remaining admissions were to pediatric subspecialty units, including pediatric intensive care unit
(ICU; preimplementation, n = 5; postimplementation, n = 6), neonatal ICU (preimplementation, n = 15; postimplementation, n = 27), cardiothoracic ICU and cardiology (preimplementation, n = 19; postimplementation, n = 18), oncology (preimplementation, n = 47; postimplementation, n = 30), bone marrow transplant (preimplementation, n = 8; postimplementation, n = 6), and other subspecialties (preimplementation, n = 3; postimplementation, n = 3). A higher proportion of BSIs in both groups presented upon admission (preimplementation, 136 of 221 [61.5%]; postimplementation, 143 of 219 [65.3%]) compared with BSI episodes acquired 48 hours after hospital admission (preimplementation, 85 of 221 [38.5%]; postimplementation, 76 of 219 [34.7%]).

Fifty-six of 221 (25.3%) BSI episodes preimplementation and 68 of 219 (31.1%) postimplementation received consultation with the infectious disease team (P = .20). Specifically, 22 of 43 (51%) and 23 of 51 (45%) S aureus BSIs (P = .68) in the preimplementation and postimplementation groups, respectively, had infectious disease consultations. Only a few BSIs caused by other gram-positive cocci had infectious disease consults in either group (preimplementation, 34 of 178, 19.1%; postimplementation, 45 of 168, 26.8%).

Pathogen Distribution

There were no significant differences in pathogen prevalence between the two groups (Table 2), including that of S aureus, E faecium, and E faecalis. The most common organism recovered—CoNS—contributed to 50% of all isolates in both groups (preimplementation, 110 of 221 [49.8%]; postimplementation, 110 of 219 [50.2%]; P = .85).

Because of the ability of the BC-GP assay to identify Staphylococcus epidemidis and the presence of the mecA gene in these isolates, the proportion of isolates reported as Staphylococcus spp. was higher in the preimplementation (91 of 221; 41.2%) versus postimplementation (42 of 219, 19.2%) (P < .001) blood cultures, whereas the proportion of isolates reported as methicillin-susceptible S epidemidis and methicillin-resistant S epidermidis was greater in postimplementation (68 of 219; 31.1%) versus preimplementation (19 of 221; 8.6%) blood cultures (P < .001).

The incidence of polymicrobial culture was similar in both groups (Table 2). All 16 of 219 target organisms (7.3%) isolated from polymicrobial samples postimplementation were identified correctly by the BC-GP assay in agreement with the results of routine identification and susceptibility testing.

Outcome

The BC-GP assay implementation significantly reduced the average time of Gram stain report to organism identification from 24.8 hours to 3.8 hours (P < .001). In addition, time from Gram stain notification to detection of methicillin-resistant S aureus, methicillin-resistant S epidermidis, and vancomycin-resistant enterococci was significantly shortened by 45.9 hours following BC-GP assay implementation (49.7 hours versus 3.8 hours; P < .001) (Figure 2).

Empiric antimicrobial therapy following blood culture collection was initiated in 188 of 221 (85.1%) infectious episodes in the preimplementation and 194 of 219 (88.6%) in the postimplementation group.

Antimicrobial optimization was indicated in 161 of 221 (72.9%) and 158 of 219 (72.1%) BSIs in the pre- and postimplementation group, respectively.

Overall, 32 of 43 (74%) episodes in the preimplementation group and 35 of 51 (69%) in the postimplementation group that grew S aureus presented indications for a treatment alteration. In methicillin-susceptible S aureus BSIs, appropriate de-escalation of therapy from vancomycin to a β-lactam agent, such as oxacillin or cefazolin, occurred in 73% (25 of 34) preimplementation and 61% (22 of 36) postimplementation patients. Suboptimal changes in the management of S aureus BSIs were made in 19% (8 of 43) of episodes preimplementation and 16% (8 of 51) postimplementation, including incidences of methicillin-susceptible S aureus bacteremia being treated with vancomycin.

Table 1. Patient Demographics and Preexisting Comorbidities

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Preimplementation, n = 194, No. (%)</th>
<th>Postimplementation, n = 189, No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M</td>
<td>119 (61.3)</td>
<td>106 (56.1)</td>
<td>.30</td>
</tr>
<tr>
<td>No documented comorbidity</td>
<td>31 (16.0)</td>
<td>32 (16.9)</td>
<td>.89</td>
</tr>
<tr>
<td>Hematologic malignancy</td>
<td>32 (16.5)</td>
<td>24 (12.7)</td>
<td>.31</td>
</tr>
<tr>
<td>Solid organ malignancy</td>
<td>15 (7.7)</td>
<td>4 (2.1)</td>
<td>.02</td>
</tr>
<tr>
<td>Hematologic disorder</td>
<td>9 (4.6)</td>
<td>12 (6.3)</td>
<td>.51</td>
</tr>
<tr>
<td>Neonatal disorder/prematurity</td>
<td>25 (12.9)</td>
<td>28 (14.8)</td>
<td>.66</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>19 (9.8)</td>
<td>29 (15.3)</td>
<td>.12</td>
</tr>
<tr>
<td>Cardiac disorder</td>
<td>28 (14.4)</td>
<td>35 (18.5)</td>
<td>.34</td>
</tr>
<tr>
<td>Respiratory disorder</td>
<td>23 (11.9)</td>
<td>23 (12.2)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>GI disorder/TPN dependenc</td>
<td>42 (21.6)</td>
<td>30 (15.9)</td>
<td>.15</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>10 (5.3)</td>
<td>12 (6.3)</td>
<td>.67</td>
</tr>
<tr>
<td>Bone/soft tissue infection</td>
<td>21 (10.8)</td>
<td>13 (6.9)</td>
<td>.21</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>0</td>
<td>3 (1.6)</td>
<td>.12</td>
</tr>
<tr>
<td>HSCTx</td>
<td>5 (2.6)</td>
<td>3 (1.6)</td>
<td>.72</td>
</tr>
<tr>
<td>Rheumatologic disorder</td>
<td>4 (2.1)</td>
<td>2 (1.1)</td>
<td>.69</td>
</tr>
<tr>
<td>Primary immune deficiency</td>
<td>2 (1.0)</td>
<td>1 (0.5)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>CVAD in situ</td>
<td>140 (63.3)</td>
<td>139 (63.5)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Blood cultures drawn from CVADa</td>
<td>111 (50.2)</td>
<td>109 (49.8)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Blood cultures drawn peripherallya</td>
<td>110 (49.8)</td>
<td>110 (50.2)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Hospital-onset BSIa, &gt;48 h</td>
<td>85 (38.5)</td>
<td>76 (34.7)</td>
<td>.43</td>
</tr>
<tr>
<td>Community-onset BSIa</td>
<td>136 (61.5)</td>
<td>143 (63.3)</td>
<td>.43</td>
</tr>
</tbody>
</table>

Abbreviations: BSI, bloodstream infection; CVAD, central venous access device; GI, gastrointestinal; HSCTx, hematopoietic stem-cell transplantation; TPN, total parenteral nutrition.

a Percentages derived from the number of blood cultures: preimplementation, n = 221; postimplementation, n = 219.
monotherapy when de-escalation to a β-lactam would have been possible. In 16 of 28 (57%) enterococcal isolates in the before and 17 of 24 (71%) isolates in the after implementation groups, antimicrobial therapy was optimized appropriately.

In the postimplementation group, mean time from Gram stain notification to antimicrobial optimization was shortened by 12.5 hours (46.6 hours versus 34.1 hours; \(P = .006\)) (Figure 2). Specifically, the mean time from Gram stain reporting to optimization of antimicrobial therapy in

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### Table 2. Gram-Positive Organisms Isolated From Blood Cultures

<table>
<thead>
<tr>
<th>Organism</th>
<th>Preimplementation, n = 221, No. (%)</th>
<th>Postimplementation, n = 219, No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>43 (19.5)</td>
<td>51 (23.3)</td>
<td>.49</td>
</tr>
<tr>
<td>MSSA</td>
<td>34 (15.4)</td>
<td>36 (16.4)</td>
<td>.79</td>
</tr>
<tr>
<td>MRSA</td>
<td>9 (4.1)</td>
<td>15 (6.8)</td>
<td>.22</td>
</tr>
<tr>
<td>CoNS</td>
<td>110 (49.8)</td>
<td>111 (50.7)</td>
<td>.85</td>
</tr>
<tr>
<td>MSSE(^a)</td>
<td>4 (1.8)</td>
<td>43 (19.6)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>MRSE(^b)</td>
<td>15 (6.8)</td>
<td>25 (11.4)</td>
<td>.10</td>
</tr>
<tr>
<td>CoNS, not speciated</td>
<td>91 (41.2)</td>
<td>42 (19.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Enterococcus lugdunensis</td>
<td>1 (0.5)</td>
<td>3 (1.4)</td>
<td>.14</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>19 (8.6)</td>
<td>23 (9.6)</td>
<td>.74</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>9 (4.1)</td>
<td>3 (1.4)</td>
<td>.12</td>
</tr>
<tr>
<td>VSE</td>
<td>6 (2.7)</td>
<td>1 (0.5)</td>
<td>.99</td>
</tr>
<tr>
<td>VRE</td>
<td>3 (1.4)</td>
<td>2 (0.9)</td>
<td>.99</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>7 (3.2)</td>
<td>3 (1.4)(^c)</td>
<td>.72</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>4 (1.8)</td>
<td>2 (0.9)</td>
<td>.69</td>
</tr>
<tr>
<td>Streptococcus agalactae</td>
<td>7 (3.2)</td>
<td>6 (2.7)</td>
<td>.88</td>
</tr>
<tr>
<td>Streptococcus spp</td>
<td>27 (12.2)</td>
<td>25 (11.4)</td>
<td>.85</td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>15 (6.8)</td>
<td>16 (7.3)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CoNS, coagulase-negative staphylococci; MRSA, methicillin-resistant Staphylococcus aureus; MRSE, methicillin-resistant Staphylococcus epidermidis; MSSA, methicillin-susceptible Staphylococcus aureus; MSSE, methicillin-susceptible Staphylococcus epidermidis; VRE, vancomycin-resistant Enterococcus faecium; VSE, vancomycin-susceptible Enterococcus faecium.

\(^a\) Coinfection within group accounting for discrepancy in numbers.

\(^b\) Because of identification of \(S\) epidermidis and the \(meA\) gene by the Verigene gram-positive blood culture assay, the proportion of isolates is reported as \(S\) aureus spp, MRSE, and MSSE.

\(^c\) One viridans streptococcal isolate was misidentified by the Verigene gram-positive blood culture assay as \(S\) pneumoniae.

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**Figure 2.** Timeline comparison of diagnostic and therapeutic interventions in the preimplementation and postimplementation periods from sample collection to antimicrobial optimization. Antimicrobial optimization is defined as de-escalation, modification, or discontinuation of antimicrobial agents. Arrows denote the mean (SD) time (in hours) from either initiation of empiric antimicrobials or reporting of Gram stain results to identification, susceptibility results, and antimicrobial optimization in the preimplementation and postimplementation groups. Abbreviation: BC-GP, gram-positive blood culture assay.
patients with *S. aureus* BSIs (Figure 3) was significantly shortened by 11.9 hours in the postimplementation group (44.2 hours versus 32.3 hours; \(P = .005\)). Similarly, time of empiric antimicrobial initiation to optimization was also shortened (63.8 hours versus 48.4 hours; \(P = .003\)). For *E. faecium* and *E. faecalis*, optimization in the postimplementation group (from Gram stain, mean 51.8 h versus 37.8 h; \(P = .16\); from empiric therapy, mean 102.4 h versus 63.4 h; \(P = .14\)) was not statistically significant (Figure 3).

For pathogens, such as *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, and viridans group streptococci (preimplementation, 25 of 221 blood cultures [11.3%]; postimplementation 18 of 219 blood cultures [8.2%]), empiric therapy was appropriate, and antimicrobial changes were not required. Thus, mean (SD) time from Gram stain report to antimicrobial optimization did not differ significantly between groups (52.4 [42] hours versus 45.9 [38] hours; \(P = .60\)).

Thirty-eight of 110 CoNS isolates (34%) in the preimplementation and 38 of 111 (35%) in the postimplementation group were considered contaminants. Faster identification of these contaminants after implementation shortened antimicrobial exposure by 39.6 hours (preimplementation median, 67.7 hours; postimplementation median, 28.1 hours; \(P = .001\)). However, no impact on LOS or hospitalization cost was demonstrated for this subgroup (Table 3).

In the postimplementation group, removal of CVAD within 14 days of bacterial identification was more frequent (11 of 111 [9.9%] versus 21 of 109 [19.3%]; \(P = .03\)), and mean time from Gram stain result to catheter removal was 5.3 days shorter (9.8 versus 4.5 days; \(P = .03\)).

Segmented linear regression analysis demonstrated no evidence of time trend in mean time to optimization in the preintervention period (\(P = .29\)), which is consistent with the notion that hospital procedures were in a steady state. Further analysis confirmed that there was a significant reduction in mean time to optimization postimplementation (\(P = .02\); \(df = 2\)), which was consistent with a −8.5 hour immediate change followed by a −0.61 h/mo further reduction.

The case mix index (preimplementation, 4.5 versus postimplementation, 4.8; \(P = .67\)) and severity index (preimplementation, 2.96 versus postimplementation, 3.16; \(P = .10\)) were similar in both groups. Overall, there was a decrease in morbidity and mortality associated with gram-positive BSIs after implementation. This is highlighted by the significant differences in median LOS seen in patients admitted to the general pediatric unit (10.4 versus 8.9 days; \(P = .04\)) and specifically in general pediatric patients with *S. aureus* BSIs (14.8 versus 9.2 days; \(P = .01\)). Analysis of median LOS from onset of BSI also demonstrated significant difference in patients admitted to general pediatric unit (10.1 versus 8.5 days; \(P = .03\)). Furthermore, significant difference in LOS from onset of BSI were also noted in all hospital admissions with *S. aureus* BSIs (15.1 versus 12.6 days; \(P = .05\)) and in general pediatric patients with *S. aureus* BSIs (14.7 versus 8.9 days; \(P = .008\)). Although not demonstrating significant difference in LOS, there was a trend toward decrease in all patients with *E. faecium*/*E. faecalis* BSIs (14.7 versus 28.1 days; \(P = .10\)) (Table 3). This is possibly due to prolonged admissions observed in patients with significant comorbidities. Crude mortality within 1 month of diagnosis of BSI was low with a trend toward lower mortality after implementation (11 of 194 [5.7%] versus 5 of 189 [2.6%]; \(P = .28\)). Need for admission to ICU was not significantly different between the two periods (79 of 194 [40.7%] versus 91 of 189 [48.1%]; \(P = .24\)).

With this decrease in morbidity and mortality, we also demonstrated a decrease in hospital costs. Similarly, this difference was most evident in the general pediatric admissions, with significant reduction in a median cost per admission by $3757 ($16 642 versus $12 885; \(P = .03\)) (mean difference, $40 290; \(P = .09\)) after implementation. Specifically, the median cost per admission decreased by $13 341 ($27 805 versus $14 464; \(P = .05\)) (mean difference, $47 613;
P = .29) in patients admitted to the general pediatric unit with S aureus BSIs. Median hospital cost was noted to be less in all hospital admissions ($35 810 versus $26 647; P = .33) (mean difference, $12 363; P = .66) and in patients with E faecium/E faecalis BSIs ($77 481 versus $67 972; P = .22) (Table 3).

**COMMENT**

Rapid laboratory diagnostic results have been shown to directly affect clinical outcome in the adult population. Our study is the first, to our knowledge, to report the impact of the BC-GP assay on outcomes in gram-positive BSIs when offered as a routine test. In addition, we are the first to report the impact of rapid laboratory diagnosis on pediatric patients. Because testing is available 24 h/d, 7 d/wk in our microbiology laboratory, our institution is in an excellent position to maximize the potential benefits of rapid molecular diagnostic strategies.

Active stewardship involving both the microbiology laboratory and the antimicrobial stewardship team is reported to be imperative for significant improvements in patient management and outcome. Perez et al reported a 31-hour decrease to time of therapy optimization when an infectious-disease pharmacist was involved. Our study used active alerting of Gram stain and BC-GP results directly to clinicians. Despite infectious-diseases involvement being limited to active consultation requests, we noted a significant decrease of 12.5 hours in time to antimicrobial optimization in the postimplementation group. Nevertheless, a mean time of 34.1 hours can still be improved. We have recently enhanced stewardship efforts by involving infectious-disease pharmacy and stewardship service, independent of consult requests for all BSIs in our institution.
Several studies have reported the positive effect of rapid testing on patient management. These studies showed that rapid identification was associated with decreased duration of hospitalization and ICU stays. Specifically, delays in appropriate antimicrobial treatment have been shown to increase mortality by greater than 3-fold and to prolong hospital LOS by at least 6 days in patients with \textit{S. aureus} BSIs.\textsuperscript{14} We reported a significant decrease in LOS of 1.6 days from onset of BSI in our general pediatric admissions and a trend toward lower mortality. Moreover, a significant decrease in LOS of 5.8 days was noted in general pediatric patients with \textit{S. aureus} BSIs.

Recovery of CoNS from blood cultures is typically considered clinically insignificant and likely contamination.\textsuperscript{23,26} A recent study\textsuperscript{27} reported suboptimal selection of empiric therapy in 23\% of CoNS BSIs. Wong et al\textsuperscript{28} showed that antimicrobial discontinuation occurred 44 hours earlier when CoNS was detected. Similarly, we demonstrated that discontinuation of antimicrobials in cases of CoNS contamination occurred 40 hours faster after implementation.

The attributable cost per BSI survivor in adults has been estimated at $6000 to $40 000 per patient.\textsuperscript{29,30} With implementation of rapid laboratory diagnostics, reported hospital cost savings range from $10 000 to $25 000 per admission.\textsuperscript{13,20} The impact of the BC-GP assay has, thus far, been assessed only in enterococcal BSIs.\textsuperscript{14} We included a broad spectrum of gram-positive bacteria identified by the BC-GP assay, and despite the findings not reaching statistical significance for all admissions and all organisms, we calculated a median cost savings of $9163 per admission. However, significant median cost savings of $13 341 per admission were reported in patients with \textit{S. aureus} BSIs admitted to the general pediatric unit.

Only a few (32 of 220; 14.5\%) CVADs were removed in both preimplementation and postimplementation groups, even when clinical status and pathogen identified presented an indication for removal. Thus, the introduction of the BC-GP assay did not dramatically increase the removal of CVADs in incidences of catheter-associated BSIs. Nevertheless, in the few cases in which CVADs were removed, removal occurred significantly faster after implementation. A limitation of the study is that our patient cohort included a high proportion of patients with complex comorbidities, and the LOS in those patients was extremely prolonged with high associated hospitalization costs. In combined analysis, no significant impact on LOS or cost was noted, a finding that was not unexpected. Other investigators encountered similar issues requiring exclusion of patients whose LOS was determined by other, institutional parameters, from LOS analysis.\textsuperscript{21} Therefore, we also analyzed LOS and cost in patients admitted to the general pediatric units. In this subanalysis, significant reductions in LOS and hospital cost were found in all patients with BSIs and in patients with \textit{S. aureus} BSIs.

This study has other limitations. Because this is a single-institution study, unique characteristics of our patient population and our institutional policies may not be applicable to other settings. Because this study used a nonrandomized design comparing 2 different periods, it may be susceptible to other unmeasured factors that could have contributed to outcome findings in the postimplementation group. To our knowledge, there were no significant changes made that affected hospitalization costs or standard of care for patients with BSI throughout either study periods, including antimicrobial stewardship practices.

Potential biases were addressed using segmented, linear analysis, which confirmed no evidence of time-trend in mean time to optimization preimplementation and evidence of significant change in optimization time after implementation, which further changed with time.

Our study highlights the importance of rapid diagnostics in the clinical microbiology laboratory and reports on its effect among pediatric patients. Implementation of the BC-GP assay contributed to a reduction in time to appropriate antimicrobial therapy, regardless of patient population, and a decrease in LOS and overall hospital costs among patients without other significant comorbidities. Further integration with the antimicrobial stewardship team may further improve time to optimal therapy and patient outcome.

We thank the following sections at Children’s Hospital Los Angeles: the ongoing efforts of the microbiology laboratory; the Financial Support Services, for providing data on hospital cost; and Petr Ponomarenko, PhD, research assistant at Computational Biology Laboratory, for assistance with statistical analysis.

References


**CAP16 Abstract Program Submission Dates Announced**

Abstract and case study submissions to the College of American Pathologists (CAP) 2016 Abstract Program will be accepted beginning on Friday, January 8 through 5 p.m. Central time Friday, March 11, 2016.

Accepted submissions will appear on the Archives of Pathology & Laboratory Medicine Web site as a Web-only supplement to the September 2016 issue. The CAP16 meeting will be held from September 25 to 28 in Las Vegas, Nevada.

Visit the CAP16 Web site (www.cap.org/cap16) for additional abstract program information as it becomes available.