Impact of Rapid Molecular Testing of Gram-Positive Blood Culture Isolates Using Verigene® Gram-Positive Blood Culture on Antimicrobial Stewardship and Clinical Outcomes within a Community Health System

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Background and Objectives
It is well known that timely increases with each additional day of inappropriate antimicrobial therapy (IAT). Newer technologies allow for rapid detection of bacteria from positive blood cultures (BCP) using an array of candidates to identify resistance genes. The Verigene Gram-positive blood culture (BCP) assay is a method for rapid identification of Gram-positive organisms and contains not only genus and species-specific targets, but also can detect three important resistance markers including macA, vanA, and vanB.

Primary Objective: To determine whether the use of Verigene® BCP results in more (1) timely initiation and adjustment of effective and appropriate antimicrobial therapy for gram-positive pathogens compared to existing microbiology testing methods (i.e., improved antimicrobial stewardship).

Secondary Objective: To determine whether the use of Verigene® BCP results in decreased hospital length of stay (LOS), total antimicrobial cost, and mortality (i.e., improved clinical outcomes).

Methods

Study Setting:
NorthShore University HealthSystem (NSUHS) is a not-for-profit healthcare organization in suburban Chicago with over 2000 affiliated physicians, 60,000 annual admissions, and 70 bedded microbiology laboratory and an electronic medical record.

Patient Selection:
All adult inpatients (age ≥ 15) with a blood culture positive for a Gram-positive bacteria by Gram stain and who were not enrolled in hospice, discharged, or transferred out of the hospital before the 72 hour mark were included in the study.

Study Design:
Quasi-experimental, pre- and post-intervention between January 2012 and August 2013. This study was reviewed by the IRB and considered exempt as a quality improvement assessment.

Microbiologic Methods:
Pre-intervention: The NSUHS has performed RT-PCR for vanA and vanB, on all positive blood cultures with a Gram stain positive of enterococcus since 2005. This test was run only once a day, 7 days per week. Conventional microbiology methods were used to identify all other bacteria as well as staphylococci, lactic acid bacteria, and enterobacteriaceae.
Post-intervention: After being validated for use in the microbiology laboratory, the Verigene GPC assay was used to test for all potential Gram-positive blood cultures as soon as time permitted. Conventional methods were used for verification of identification and susceptibility testing.

Methods (continued)

Antimicrobial Stewardship Method:
Pre-intervention: The microbiology lab notified the infectious diseases physicians with the results of their panel for ten days until for staphylococci isolates upon completion. For patients with non-staphylococcal/positive blood culture results, pharmacists received an EPIC alert through electronic medical record (EMR) notification triggering them to a positive blood culture result. Upon receipt of the notification from the microbiology laboratory or the EPIC alert, the pharmacists notified the primary team to assist with antimicrobial adjustment.

Post-intervention: All methods from pre-intervention continued with one exception. The microbiology lab notified the infectious diseases physicians with the results of the Verigene BCP assay as the EMR replaced the pharmacists. The pharmacists then notified the primary team to assist with antimicrobial adjustment.

Patient Data Collection:
Retrospective chart review was conducted on 500 inpatients (250 pre-intervention (Group 1) and 250 post-intervention (Group 2)). Patient data was collected and used for statistical matching of patients in the two groups including Age, Sex, BMI, APACHE II, Charlson Score, hospitalization in the last 90 days, ICU admission, comorbid conditions including cancer, active methicillin-resistant organisms or organisms resistant to receipt, chronic lung disease, liver disease, chronic liver disease, cerebrovascular disease. Only patients with Gram-positive blood culture collection to effective antimicrobial therapy, time from blood culture to optimal therapy measured in days, total antimicrobial cost, mortality, hospital length of stay (LOS), ICU LOS.

Definitives:
Effective antimicrobial therapy was defined as any antibiotic that would cover the organism that was ultimately suspected and any other concomitant infections. Optimal antimicrobial therapy was defined as any antibiotic that would cover the organism ultimately isolated and any other concomitant infection(s), or in the case of a blood culture, the patient was ultimately sent to the intensive care unit and/or was on intravenous antibiotic therapy.

Laboratory Data Collection:
Time of blood culture collection, time of Gram stain report, time of molecular testing from the blood culture, and time of susceptibility testing was collected for comparison.

Analysis:
Group 1 (pre-intervention) and Group 2 (post-intervention) were statistically matched using propensity scoring. Continuous variables were compared using a two-sample t-test and categorical variables were compared using a chi-squared test.

Results

Of the 500 patients screened for inclusion, 390 (181 pre-intervention and 209 post-intervention) patients met inclusion criteria and underwent propensity matching based on age, diabetes and mortality. It was found there was no difference in the times from blood culture collection to Gram stain report or susceptibility test results.

Table 2: Patient characteristics used for propensity scoring and matching between the pre- and post-intervention groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-Intervention</th>
<th>Post-Intervention</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70.3 ± 14.5</td>
<td>70.9 ± 14.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.0 ± 3.8</td>
<td>20.4 ± 3.7</td>
</tr>
<tr>
<td>Charlson Score</td>
<td>5.6 ± 3.3</td>
<td>5.7 ± 3.3</td>
</tr>
<tr>
<td>APACHE II</td>
<td>13.3 ± 5.2</td>
<td>13.4 ± 5.2</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>6.4 ± 2.5</td>
<td>6.2 ± 2.3</td>
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</tbody>
</table>

Table 3: Clinical outcomes of interest pre- and post-intervention in 120 matched patient pairs.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-Intervention</th>
<th>Post-Intervention</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in infection rate</td>
<td>0.08</td>
<td>0.08</td>
<td>0.000</td>
</tr>
<tr>
<td>Change in mortality rate</td>
<td>0.05</td>
<td>0.05</td>
<td>0.000</td>
</tr>
<tr>
<td>Change in LOS</td>
<td>2.2 ± 1.5</td>
<td>2.1 ± 1.6</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Table 4: Laboratory turn-around times for outcomes of interest pre- and post-intervention.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-Intervention</th>
<th>Post-Intervention</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to isolate</td>
<td>3.8 ± 1.7</td>
<td>2.4 ± 0.8</td>
<td>0.000</td>
</tr>
<tr>
<td>Time to identification</td>
<td>3.8 ± 1.7</td>
<td>2.4 ± 0.8</td>
<td>0.000</td>
</tr>
<tr>
<td>Time to susceptibility</td>
<td>3.8 ± 1.7</td>
<td>2.4 ± 0.8</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Discussion

• The use of Verigene BC-GP was associated with a modelled improvement (10 hours) in reducing the time to optimal antimicrobial therapy for patients with blood culture positive for Gram-positive organisms.

• This outcome may be attributed to 1) the ability to perform the Verigene assay as needed (one step kit) and 2) the ability of the Verigene assay to perform the vanA and vanB tests than staphylococci when compared to our existing molecular methods.

• Prior-studies evaluating clinical and stewardship outcomes related to rapid microbial diagnostic did not have an existing stewardship framework in place or advanced molecular technology was not found in the case of interest including time from blood culture collection to effective antimicrobial therapy, thus the benefit of improved to optimal therapy seemed becomes more relevant in this study.

• Limitations of the study include small sample size, retrospective nature; however, propensity scoring was done to mitigate the above limitations.

• Additional improvements that can be made to reduce the time to blood culture collection to optimal antibiotic therapy may include utilizing existing electronic data modules to notify the clinicians immediately.

• There were no differences in significant clinical outcomes of interest, however, this is likely related to the lack of difference in the studies being done at different sites and different years.

For the microbiology lab not advanced in house molecular diagnostics and an active stewardship program, the use of the Verigene BC-GP test may even have larger benefits.

References