Improving time to optimal *Staphylococcus aureus* treatment using a penicillin-binding protein 2a assay

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The penicillin-binding protein 2a (PBP2a) assay is a quick, accurate and inexpensive test for determining methicillin susceptibility in *Staphylococcus aureus*. A pre–post-study design was conducted using a PBP2a assay with and without the impact of an antimicrobial stewardship intervention to improve time to optimal therapy for methicillin-susceptible and methicillin-resistant *S. aureus* isolates. Our results demonstrate significantly improved time to optimal therapy and support the use of a PBP2a assay as part of an AS programme for all healthcare facilities, especially those with limited resources.

INTRODUCTION

A growing body of evidence supports the use of rapid diagnostic tests to shorten time to appropriate antimicrobial therapy and improve patient outcomes by reducing antimicrobial usage, hospital length of stay, mortality and overall hospital expenditures (Forrest et al., 2006; Brown & Paladino, 2010; Nicolsen et al., 2013). As a result, recommendations for implementing a successful antimicrobial stewardship (AS) programme include incorporating rapid diagnostic tests to use and support stewardship efforts (The Joint Commission, 2013; Bauer et al., 2014; CDC, 2014). A variety of molecular assays for rapid identification of target organisms are commercially available. However, these molecular assays may not be affordable for many healthcare facilities looking to initiate an AS programme. Simple, inexpensive rapid diagnostic tools that provide real-time testing with random access may be more practical for healthcare facilities, particularly those with limited resources (Mosammaparast et al., 2012).

Detection of either the *mecA* gene or the low-affinity penicillin-binding protein 2a (PBP2a) has been shown to accurately identify methicillin resistance in *Staphylococcus aureus* (MRSA) and is recommended by the CLSI (2016). The PBP2a immunochromatographic assay (Alere, 2016) offers ease of use and random access testing with rapid identification of methicillin resistance from pure colonies of *S. aureus* in 5 min versus 24 h or longer using conventional methods. There are several reasons why we investigated the use of a PBP2a assay for early detection of *S. aureus* susceptibility: (1) it is imperative to administer appropriate and timely antimicrobials for patients with *S. aureus* bacteraemia (Bauer et al., 2010); (2) methicillin-susceptible *S. aureus* (MSSA) is adding to the burden of MRSA infections with appreciable mortality (Cosgrove et al., 2003); (3) optimal treatment options have become more clearly defined for MRSA and MSSA, vancomycin being the first-line antibiotic of choice for MRSA and anti-staphylococcal β-lactams (e.g. cefazolin and oxacillin) for MSSA (Schweizer et al., 2011); and (4) the PBP2a assay offers a rapid, accurate and inexpensive method for detecting methicillin resistance in clinical *S. aureus* isolates, which consequently allows for more timely initiation of optimal antibiotics. (Portions of this paper were presented at the 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy, 10–13 September 2013, Denver, Colorado.)
METHODS

A controlled pre-post, quality improvement study was conducted to assess the impact of a PBP2a assay with or without an active AS intervention to improve time to optimal therapy for MRSA and MSSA isolates. This study was conducted at the Rush University Medical Center in Chicago, Illinois. The Rush University Medical Center and Midwestern University institutional review boards approved the study methods with waiver of informed consent.

During phase 1 (pre-PBP2a testing) of the study from January 2012 to June 2012, susceptibility testing of *S. aureus* isolates with adequate number of colonies from any source of hospitalized patients was performed using the gold standard cefoxitin disc test. From January 2013 to July 2013, methicillin susceptibility testing of inpatient isolates was also performed using the PBP2a assay according to the manufacturer’s instructions with or without an AS intervention (phase 2, post-PBP2a). Patients were included once, and the earliest confirmed *S. aureus* culture during an admission period was assessed for susceptibility. Patients with *S. aureus* isolates were excluded from the study if (1) younger than 18 years, (2) a β-lactam allergy was documented, (3) hospitalized for less than 48 h, (4) colonized with MRSA from a nasal swab or (5) need for broad-spectrum antimicrobial coverage beyond final culture results was warranted (e.g. polymicrobial infections). The primary objective of this study was to assess time to optimal therapy for MRSA and MSSA isolates using the rapid PBP2a assay in phase 2 compared to phase 1. Our secondary objective was to assess the impact of an active AS intervention in addition to PBP2a testing to further improve time to optimal therapy in the phase 2 cohort. Time to optimal therapy was defined as the time in hours from culture collection to the recorded time of the first dose of an anti-staphylococcal β-lactam agent for MSSA or vancomycin for MRSA and time to de-escalation of unnecessary empiric broad-spectrum antibiotics with both Gram-positive and Gram-negative activity such as piperacillin-tazobactam.

An email communication of the study objectives and report of the PBP2a results in the electronic medical records was provided to all physicians and pharmacists. Trained microbiology staff performed the PBP2a assay between 6 am and 3 pm daily. Results of the PBP2a assay were reported in the electronic medical records as follows: ‘MSSA or MRSA based on results of PBP2a test. Final susceptibility results to follow’. Assessment of time to optimal therapy using the PBP2a assay without an AS intervention was conducted from January 2013 to March 2013. From April 2013 to July 2013, an active AS intervention was conducted by an infectious diseases physician or pharmacist, who directly communicated results of the PBP2a assay to the primary service and recommended optimization of therapy (e.g. discontinuation of vancomycin for MSSA and/or discontinuation of broad-spectrum antibiotic therapy).

Statistical analysis was performed using SPSS version 22. Categorical data were analysed using a chi-square or Fisher’s exact test, and Student’s t-test and the Wilcoxon rank sum test were used for continuous variables where appropriate. A $P$ value set at $0.05$ was deemed statistically significant. The sensitivity, specificity, positive predictive value and negative predictive value of the PBP2a assay for early detection of *S. aureus* susceptibility were calculated using standard statistics. The efficient score method, corrected for continuity, was used to calculate 95% confidence intervals (CIs) (Newcombe, 1998). Calculations were performed using VassarStats, a web-based statistical software (www.vassarstats.net; accessed 30 July 2016).

### RESULTS AND DISCUSSION

Sixty-nine *S. aureus* isolates were included in phase 1, and 71 were included in phase 2 of the study. Patient demographics (age and gender) and characteristics were found to be similar between the two groups (Table 1). MSSA was the dominant *S. aureus* isolate, representing approximately two-thirds of isolates for both phase 1 [MSSA, 46 isolates (67%); MRSA, 23 isolates (33%)] and phase 2 [MSSA, 47 isolates (66%); MRSA, 24 isolates (34%)]. Common culture sources during the study were blood, wounds and abscesses and joint fluid, followed by sputum and bronchial lavage. The mean length of hospital stay in phase 1 was slightly longer at 13.9 days compared to 10.8 days for phase 2 ($P=0.18$).

The mean time to culture identification during phase 2 was 33.4 h, a significant reduction from 60.9 h in phase 1 when using conventional testing with cefoxitin disc ($P<0.0001$) (Table 2). Mean time to optimal therapy for phase 1 and phase 2 (without AS intervention) was 72.2 and 44.7 h, respectively ($P<0.0001$). As shown in Table 2 and Fig. 1, inclusion of an active AS intervention during phase 2 further decreased time to optimal therapy to 38.7 h ($n=47$). Three false-positive results using the PBP2a assay were identified during the study period. Investigation of the results concluded that the test strips were left in the assay tube longer than the manufacturer-recommended 5 min. Retesting at the 5 min mark resulted in consistent findings with the conventional method. Statistical analyses accounted for the three false-positive results using the PBP2a assay. Thus, the PBP2a assay demonstrated a sensitivity of 100% (95% CI, 80.7%–100%), a specificity of 94% (95% CI, 82.4%–98.4%), a positive predictive value of 87.5% (95% CI, 66.5%–96.7%) and a negative predictive value of 100% (95% CI, 90.5%–100%). However, with precise technique, the validity of the PBP2a assay was 100% for detecting *S. aureus* methicillin susceptibility when compared to conventional methods using the cefoxitin disc test.

### Table 1. Patient demographics and characteristics

<table>
<thead>
<tr>
<th></th>
<th>Phase 1, $n=69$ (%)</th>
<th>Phase 2, $n=71$ (%)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>32 (46)</td>
<td>40 (56)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>S. aureus susceptibility</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSA</td>
<td>46 (67)</td>
<td>47 (66)</td>
<td>NS</td>
</tr>
<tr>
<td>MRSA</td>
<td>23 (33)</td>
<td>24 (34)</td>
<td></td>
</tr>
<tr>
<td><strong>Culture site</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>25 (36)</td>
<td>39 (55)</td>
<td>NS</td>
</tr>
<tr>
<td>Joint</td>
<td>10 (15)</td>
<td>10 (14)</td>
<td></td>
</tr>
<tr>
<td>Sputum/BAL</td>
<td>6 (9)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Wound/abscess</td>
<td>21 (30)</td>
<td>15 (21)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7 (10)</td>
<td>6 (9)</td>
<td></td>
</tr>
<tr>
<td><strong>Length of hospital stay (days)</strong></td>
<td>13.9±16.8</td>
<td>10.8±9.7</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Phase 1, Pre-PBP2a; phase 2, post-PBP2a; NS, not significant.
Our pre–post PBP2a study showed a significant reduction in time to optimal therapy for *S. aureus* infections. Accuracy of the rapid PBP2a assay, using precise technique, was 100% for MSSA and MRSA study isolates from any site of infection when confirmed by the follow-up conventional cefoxitin disc test. Like other studies, we too observed a clear benefit of incorporating active AS interventions (Brown & Paladino, 2010; Bauer et al., 2010, 2014), as further reduction in time to optimal therapy was observed.

Effective from 1 January 2017, accredited hospitals, critical access hospitals and nursing care centres in the USA will be held accountable to the new medication management standard proposed by The Joint Commission, introducing elements of performance for an identifiable AS programme (The Joint Commission, 2016). Implementation of policies and interventions to support optimal antibiotic use is a core element of the new standard. As eluded earlier, use of rapid diagnostic tests can improve antimicrobial use and support AS efforts (The Joint Commission, 2013; Bauer et al., 2014; CDC, 2014). Developing a new AS programme in compliance with the new AS elements of performance will bring challenges, particularly for facilities limited by resources and personnel. Our experience showcases the value of

### Table 2. Time to culture results and optimal therapy: phase 1 versus phase 2 with and without AS intervention

<table>
<thead>
<tr>
<th>Study phase (n)</th>
<th>Time to final culture using conventional method*, mean ±SD (range), hours</th>
<th>Time to PBP2a result†, mean ±SD (range), hours</th>
<th>Time to optimal therapy‡, mean ±SD (range), hours</th>
<th>P value</th>
<th>Time to optimal therapy§, mean ±SD (range), hours</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 (69)</td>
<td>63.4±19.4 (40–127)</td>
<td>72.2±38.8 (11–245)</td>
<td>72.2±38.8 (11–245)</td>
<td></td>
<td>72.2±38.8 (11–245)</td>
<td></td>
</tr>
<tr>
<td>Phase 2 (71)</td>
<td>60.9±14 (37–100)</td>
<td>33.4±12.7 (14–75)</td>
<td>38.7±15 (1–75)</td>
<td>0.08</td>
<td>38.7±15 (1–75)</td>
<td>0.08</td>
</tr>
<tr>
<td>P value</td>
<td>NS</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td>&lt;0.0001</td>
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</tbody>
</table>

Phase 1, pre-PBP2a; phase 2, post-PBP2a; NS, not significant.
*Time (hours) from earliest reported culture collection to earliest reported final culture result.
†Time (hours) from earliest reported culture collection to the time of reported PBP2a result.
‡Time (hours) from earliest reported culture collection to the start of optimal antibiotic therapy.
§Active AS intervention by an ID physician or pharmacist based on PBP2a results; n=47.

*Fig. 1.* Mean time to optimal therapy: phase 1 versus phase 2 with and without AS intervention. *Time to optimal therapy was defined as the time in hours from culture collection to the recorded time of the first dose of an anti-staphylococcal β-lactam for MSSA infections and time to de-escalation or discontinuation of the empiric Gram-negative agent for MRSA infections when concurrent Gram-negative infection was not suspected. Phase 1, pre-PBP2a; phase 2, post-PBP2a.
the PBP2a assay as a rapid diagnostic tool and its potential compared to some rapid molecular diagnostic assays, which may require batch testing and purchase of expensive equipment and testing reagents. The cost of each PBP2a assay, at the time of this study, was approximately $12.

The PBP2a assay is able to provide an accurate, rapid and cost-effective option for healthcare facilities, including those with limited laboratory resources who are seeking to introduce rapid diagnostic tools to support regulatory AS programmes. The PBP2a assay continues to be a valuable tool at our institution for early detection of *S. aureus* susceptibility and improving time to optimal antimicrobial therapy as an AS policy and intervention.

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**REFERENCES**


