Impact of Results of a Rapid *Staphylococcus aureus* Diagnostic Test on Prescribing of Antibiotics for Patients with Clustered Gram-Positive Cocci in Blood Cultures

Jane Davies,a,b* Claire L. Gordon,a,b* Steven Y. C. Tong,a,c Robert W. Baird,b and Joshua S. Davisa,c

Department of Infectious Diseases, Royal Darwin Hospital, Darwin, Australiaa; Department of Microbiology, Royal Darwin Hospital, Darwin, Australiab; and Menzies School of Health Research and Charles Darwin University, Darwin, Australiac

In tropical northern Australia, approximately 20% of *Staphylococcus aureus* bacteremia is caused by methicillin-resistant *Staphylococcus aureus* (MRSA). We prospectively evaluated the impact on clinician antibiotic prescribing of the results obtained from performing the GeneXpert MRSA/SA test on 151 positive blood cultures with clustered Gram-positive cocci. The GeneXpert result led to earlier appropriate prescription of vancomycin for 54% of patients with MRSA; 25% of patients avoided vancomycin, and 16% of patients had all antibiotics ceased.

Community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is becoming increasingly prevalent in many parts of the world (3), including northern Australia (11). When a positive blood culture (BC) reveals Gram-positive cocci in clusters (GPCC), the choice of initial antibiotics is a balance between breadth of coverage for the likely pathogen and avoidance of unnecessary antibiotic use. From the time a blood culture signals positive, oxacillin susceptibility testing for *S. aureus* can take as long as 48 h using standard laboratory methods or as little as 90 min for targeted molecular methods (4, 5, 7, 8, 10, 12). There are few prospective studies investigating whether the earlier knowledge of a MRSA, methicillin-susceptible *S. aureus* (MSSA), or coagulase-negative staphylococcus (CNS) isolate influences antibiotic prescribing (9).

We prospectively evaluated the impact on clinician antibiotic prescribing of using the second-generation GeneXpert Xpert MRSA/SA BC test (hereinafter “the GeneXpert”); Cepheid, Sunnyvale, CA) on all positive BCs (BacT/Alert system; bioMérieux, Durham, NC) containing GPCCs between December 2010 and July 2011. In addition, we investigated laboratory factors that may predict an *S. aureus* bacteremia rather than a CNS bacteremia. Inclusion criteria included an age of 18 years or above, time from collection to positivity of less than 48 h, and no previous positive BCs with GPCCs in the past 30 days.

BCs with GPCCs were tested using the second-generation GeneXpert according to the manufacturer’s instructions. The second-generation GeneXpert was validated against the first-generation GeneXpert using 24 BCs with GPCCs (100% concordance), and thereafter, only the second-generation GeneXpert was used. In addition, BCs with GPCCs were also processed according to standard laboratory procedures, including the use of the Vitek 2 (bioMérieux, Durham, NC) for identification and antibiotic susceptibility testing (11). MRSA isolates were defined as nonmultiresistant or multiresistant as described previously (11).

After GPCCs were detected in BC fluid, the treating physician was contacted throughout the working day (0800 to 1600) by telephone and informed of this. For those BCs which flagged out of hours, the clinician was contacted at 0800 the next day. Using a structured questionnaire, the clinician was asked for current antibiotic therapy and what antibiotics they would prescribe based on the Gram stain result. They were then informed of the GeneXpert result and asked what antibiotics they would now prescribe. Antibiotics considered appropriate for MRSA included vancomycin or teicoplanin and for MSSA included cefazolin, flucloxacillin, piperacillin-tazobactam, ticarcillin-clavulanic acid, meropenem, teicoplanin, and vancomycin.

Approval was obtained from the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (approval HREC-2010-1436). Proportions were compared using Fisher’s exact test and continuous measures using Student’s t test or rank-sum test for normally distributed and nonparametric data, respectively, using STATA, version 11.0 (StataCorp, College Station, TX). A P value of ≤0.05 was considered significant.

One hundred fifty-one patients had a BC with GPCCs (Table 1), of which 33 (22%) were confirmed to be *S. aureus*. Several genetic variants of *S. aureus* occur in our region (including the phylogenetically divergent clonal complex 75) (11); however, the GeneXpert was able to detect all *S. aureus* isolates. Four CNSs gave an invalid result on the GeneXpert, which was due to the operator error of adding too much BC fluid. Compared with the phenotypic result, the sensitivity and specificity of the second-generation GeneXpert for differentiating *S. aureus* from non-*S. aureus* isolates were 100% and 96.7%, respectively (when invalid results were considered to be false positives), similar to previous reports for the first-generation product (5, 7, 12).

Before the BC became positive, only 30% of patients with *S. aureus* bacteremia were receiving appropriate antibiotics (Table 2). Following notification of only the Gram stain result to the...
TABLE 1 Clinical and laboratory characteristics of patients with clustered Gram-positive cocci isolated from blood cultures

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Coagulase-negative Staphylococcus isolates (n = 118)</th>
<th>S. aureus isolates (n = 33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male [no. (%)]</td>
<td>46 (39)</td>
<td>19 (58)</td>
<td>0.044</td>
</tr>
<tr>
<td>Yr of age [median (IQR)]</td>
<td>53 (43–69)</td>
<td>56 (44–60)</td>
<td>0.97</td>
</tr>
<tr>
<td>Reason BC taken*</td>
<td>70 (60)</td>
<td>26 (81)</td>
<td>0.021</td>
</tr>
<tr>
<td>Fever [no. (%)]</td>
<td>46 (40)</td>
<td>6 (19)</td>
<td>0.021</td>
</tr>
<tr>
<td>BC taken &gt;2 days after admission [no. (%)]</td>
<td>14 (12)</td>
<td>7 (21)</td>
<td>0.14</td>
</tr>
<tr>
<td>Neutrophil count [median (IQR)]</td>
<td>109/cell/liter</td>
<td>118 (14–18)</td>
<td>0.09</td>
</tr>
<tr>
<td>White cell count × 10³/cell [median (IQR)]</td>
<td>8 (7–12)</td>
<td>91 (37–152)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

* MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-susceptible Staphylococcus aureus; BC, blood culture; IQR, interquartile range.

The number of patients in the non-S. aureus group was 116, and the number in the S. aureus group was 33.

TABLE 2 Clinician antibiotic prescribing before and after the results of GeneXpert

<table>
<thead>
<tr>
<th>Antibiotic prescribingb</th>
<th>Non-S. aureus isolates (n = 118)</th>
<th>S. aureus isolates (n = 33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>On appropriate antibiotics when BC flagged positive</td>
<td>5d</td>
<td>9</td>
<td>0.002</td>
</tr>
<tr>
<td>Clinician decided on appropriate antibiotics after the result of BC</td>
<td>10d</td>
<td>21d</td>
<td>0.56</td>
</tr>
<tr>
<td>On appropriate antibiotics after result of Xpert MRSA/SA BC</td>
<td>50</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

* MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-susceptible Staphylococcus aureus; BC, blood culture.

b Antibiotics considered appropriate for MRSA included vancomycin and for MSSA included cephalazolin, flucloxacillin, piperacillin-tazobactam, ticarcillin-clavulanic acid, meropenem, teicoplanin, and vancomycin.

c There were 9 nonmultiresistant MRSA isolates and 2 multiresistant MRSA isolates.

d Two patients with S. aureus bacteremia had antibiotic treatment withdrawn for reasons of palliative care (one with MRSA and one with MSSA).

Rapid Identification of S. aureus and Antibiotic Prescribing

A rapid test for identifying Staphylococcus aureus in blood cultures could be a valuable tool in the management of patients with suspected S. aureus bacteremia. The GeneXpert test, a rapid molecular test for the detection of S. aureus, was evaluated in a recent study to determine its effectiveness in guiding antibiotic prescribing.

The study involved 151 patients with suspected S. aureus bacteremia, all of whom had a blood culture (BC) flagged positive. The GeneXpert test was performed on each BC, and the results were compared with the antibiotic prescribing before and after the test.

The results showed that the GeneXpert test significantly influenced antibiotic prescribing. For non-S. aureus bacteremia, only 5% of patients had appropriate antibiotics prescribed before the test, compared to 9% after the test (P = 0.002). For S. aureus bacteremia, 10% of patients had appropriate antibiotics prescribed before the test, compared to 21% after the test (P = 0.56).

The study also showed that the GeneXpert test reduced the time to positivity of BCs. The mean time to positivity was 22 h (IQR: 14–19) for patients with non-S. aureus bacteremia and 9 h (IQR: 37–152) for patients with S. aureus bacteremia, with a statistically significant difference (P < 0.001).

The use of the GeneXpert test in this study is likely to have been cost effective, although a formal cost analysis was not an original aim of the study, but it is likely to have been cost effective, although a formal cost analysis was not an original aim of the study, assuming that the time taken for GPCCs to be identified as S. aureus or CNS is 24 h, the cost of a GeneXpert kit is $85, the cost of a bed day is $1,168, and the cost of vancomycin is $30 per day, the use of the GeneXpert in our 151 patients led to net savings.

In conclusion, the GeneXpert test is a rapid and easy-to-use tool for identifying S. aureus in blood cultures, leading to more appropriate antibiotic prescribing and potentially reducing the time to positivity of BCs.
savings of $16,637 over a 7-month period. Our cost analysis is limited in being an inferred estimate of reductions in antibiotic use, hospital stay, and drug administration. Therefore, it probably underestimates the true cost effectiveness of using a rapid PCR test. For example, Bauer et al. also demonstrated that the introduction of a rapid PCR MRSA/SA BC test resulted in timely and effective therapy and that it decreased length of stay and hospital costs (1).

A further limitation of this study is the time lag in liaising with treating clinicians regarding results that flagged positive outside standard working hours. The impact on antibiotic prescribing and cost savings may therefore be greater than we have reported if the assay were performed 24 h a day. However, our results reflect the real-world setting of a laboratory where it is not feasible to provide such a rapid diagnostic modality outside working hours.

Early identification of S. aureus isolates, including MRSA, using the GeneXpert reduces unnecessary prescription of antibiotics and increases the likelihood that patients with MRSA will receive early appropriate vancomycin therapy.

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REFERENCES