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

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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

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TABLE 1 Clinical and laboratory characteristics of patients with clustered Gram-positive cocci isolated from blood cultures[a]

Patient characteristic	Patients with clustered Gram-positive cocci isolated from BCs ($n = 151$)		
	Coagulase-negative *Staphylococcus* isolates ($n = 118$)	*S. aureus* isolates ($n = 33$)	*P* value
Male [no. (%)]	46 (39)	19 (58)	0.044
Yr of age [median (IQR)]	53 (43–69)	56 (44–60)	0.97
Reason BC taken[b]			
Fever [no. (%)]	70 (60)	26 (81)	0.021
Suspected infection without fever [no. (%)]	46 (40)	6 (19)	0.021
BC taken >2 days after admission [no. (%)]	14 (12)	7 (21)[c]	0.14
Laboratory characteristics			
Time (h) to BC positivity [median (IQR)][d]	22 (20–26)	15 (14–19)	<0.001
Time-to-positivity less than 24 h [no. (%)][d]	52 (60)	22 (92)	0.002
Two of 2 BC bottles positive [no. (%)]	33 (28)	23 (70)	<0.001
C-reactive protein [median (IQR)]	51 (18–121)	91 (37–152)	0.09
White cell count $\times 10^9$/liter [median (IQR)]	11 (8–15)	13 (8–17)	0.30
Neutrophil count $\times 10^9$/liter [median (IQR)]	8 (5–12)	11 (7–14)	0.18

[a] MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; BC, blood culture; IQR, interquartile range.
[b] The number of patients in the non-*S. aureus* group was 116, and the number in the *S. aureus* group was 32.
[c] Includes 2 patients with MSSA and 5 patients with MRSA.
[d] Time-to-positivity data were available for 110 patients.

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

Antibiotic prescribing[b]	Non-*S. aureus* isolates ($n = 118$)	*S. aureus* isolates ($n = 33$)		
		MRSA ($n = 11$)[c]	MSSA ($n = 22$)	*P* value
On appropriate antibiotics when BC flagged positive		1	9	0.066
Clinician decided on appropriate antibiotics after the result of BC Gram stain		5[d]	21[d]	0.002
On appropriate antibiotics after result of Xpert MRSA/SA BC		10[d]	21[d]	0.56
Compared to the chosen antibiotic after the Gram stain, clinician antibiotic choice changed following Xpert MRSA/SA BC result	50	5	10	

[a] 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 cephazolin, flucloxacillin, pipercillin-tazobactam, ticlarcillin-clavulanic acid, meropenem, teicoplanin, and vancomycin.
[c] There were 9 nonmultiresistant MRSA isolates and 2 multiresistant MRSA isolates. One BC cultured both multiresistant MRSA and MSSA and was included in the MRSA group.
[d] Two patients with *S. aureus* bacteremia had antibiotic treatment withdrawn for reasons of palliative care (one with MRSA and one with MSSA).

clinician, nearly all patients with MSSA bacteremia would have been prescribed an appropriate antibiotic, while only 46% of patients who cultured MRSA would have been. Following notification of the GeneXpert result, all patients with MRSA were appropriately prescribed vancomycin. A GeneXpert result of either MSSA or CNS resulted in 36 patients appropriately avoiding vancomycin after the BC became positive. Compared to the antibiotics the clinician would have prescribed following the Gram stain result, 64/151 patients (42%) had a different antibiotic regimen prescribed following the knowledge of the GeneXpert result, including 24/151 patients (16%) with CNS who had antibiotics stopped completely.

In comparison to patients with CNS isolated, patients with *S. aureus* bacteremia were more likely to be male (odds ratio [OR], 2.12; 95% confidence interval [95% CI], 1.0 to 4.7), have a history of fever at the time the BC was taken (OR, 2.8; 95% CI, 1.0 to 7.4), and have both BC bottles positive (OR. 5.9; 95% CI. 2.4 to 14.7). BC bottles culturing *S. aureus* signaled positive earlier than BCs culturing CNS, with 92% (22/24) of *S. aureus* BCs signaling positive within 24 h compared with 60% (52/86) of CNS (OR, 7.2; 95% CI, 1.5 to 34.9) (Table 1).

The proportion of *S. aureus* bacteremia due to MRSA was higher in our study (31%) than in earlier reports but is consistent with the gradual increase in local MRSA bacteremia previously reported (11). We found the second-generation GeneXpert accurate and easy to use (sensitivity, 100%; specificity, 96.7%). There were no false-positive results due to mixed MSSA (empty cassette variant) or methicillin-resistant CNS documented, although this is a recognized limitation of this assay (12). Compared with the Gram stain result, knowledge of the GeneXpert result increased the proportion of MRSA bacteremia patients appropriately receiving vancomycin from 46% to 100%, confirming that the GeneXpert resulted in more accurate and timely antibiotic prescribing for those patients with MRSA bacteremia.

Another option with rising MRSA rates would be to empirically commence vancomycin in all patients with GPCC in a BC. Economic analysis has shown that rapid PCR testing for MRSA has the potential to reduce mortality rates and be substantially cheaper than empirical vancomycin across the United States and Europe at a wide range of different MRSA prevalence rates (2). Our data appear consistent with this; knowing the GeneXpert result led to 27% (41/151) of our study population avoiding vancomycin completely. Just over a third of patients changed antibiotics following the notification of the GeneXpert result (50 patients with CNS, 5 patients with MRSA, and 10 patients with MSSA), including 16% in whom antibiotics were stopped completely. The use of the GeneXpert in our center is likely to have been cost effective, although a formal cost analysis was not an original aim of our 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 (6), and the cost of vancomycin is $30 per day, the use of the GeneXpert in our 151 patients led to net

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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