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Impact of rapid mecA polymerase chain reaction rapid diagnostic testing for Staphylococcus aureus in a pediatric setting

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Abstract

Rapid molecular technology can detect the mecA resistance gene in *Staphylococcus aureus* (SA), predicting methicillin susceptibility in under one hour. In combination with antimicrobial stewardship program interventions in adults with SA bacteremia, rapid mecA testing decreases time to targeted therapy. This intervention has not yet been shown effective in pediatric patients or in the absence of real-time stewardship interventions. The objective of this study was to determine if time to optimal therapy decreased following implementation of GeneXpert rapid diagnostic testing (RDT) in a pediatric institution without a formal antimicrobial stewardship protocol for response. The primary outcome was time to optimal therapy, determined by the number of hours from collection of the blood sample to the initiation of an optimal regimen. Optimal regimens were defined as vancomycin therapy alone for MRSA and nafcillin, oxacillin, or cefazolin alone for MSSA.

Background

Vancomycin is usually included in empiric antimicrobial regimens to account for potential resistance when *Staphylococcus aureus* (SA) bacteremia is suspected. Once organism identification and susceptibility are known, therapy can be optimized to target the isolated bacteria, including discontinuation of vancomycin when methicillin-susceptible *Staphylococcus aureus* (MSSA) is present. Prolonged vancomycin exposure is associated with the risk of renal dysfunction and the development of resistance. The widespread use of vancomycin to treat methicillin-resistant *Staphylococcus aureus* (MRSA) has coincided with an increased incidence of vancomycin-resistant enterococci infections.[1-4] Additionally, vancomycin treatment failure has been associated with the increased incidence of heterogenous vancomycin-intermediate SA.[5] Minimal use of unnecessary vancomycin is advised to prevent the emergence of resistance.[6-7]

Beyond the risks associated with vancomycin therapy, optimizing directed therapy for MSSA bacteremia may be associated with improved outcomes. Vancomycin monotherapy may be inferior to a beta-lactam antibiotic alone or in combination with vancomycin in the empiric treatment of MSSA bacteremia, resulting in delayed culture clearance, relapse, or infection-related mortality.[8-11] Patients initiated on vancomycin and switched to nafcillin or cefazolin for completion of therapy were 69% less likely than patients continued on vancomycin alone to die from the MSSA infection.[12]

The GeneXpert MRSA/SA BC (Cepheid, Sunnyvale, CA) is a rapid diagnostic test (RDT) which uses polymerase chain reaction (PCR) assaying technology to detect the presence of the *Staphylococcus aureus* mecA gene in positive blood cultures. The mecA gene codes for methicillin resistance via mutation of a penicillin binding protein

which has decreased binding affinity to beta-lactam antibiotics. The result is differentiation between MSSA and MRSA in blood culture specimens in less than one hour as opposed to traditional methods which may take an additional 18 to 48 hours.[13] Prior to GeneXpert implementation, the identification of staphylococcal isolates from blood cultures was based solely on phenotypic analysis (VITEK 2; bioMérieux) or proteomic profiling (Bruker MALDI biotyper; Bruker) of colonies grown in subculture of the positive broths. Phenotypic testing by either VITEK 2 or Etest (bioMérieux) was used to determine the antimicrobial susceptibility profiles of isolates in both time periods. In combination with antimicrobial stewardship program interventions in adult patients with SA bacteremia, rapid PCR testing decreases total hospital costs, pharmacy specific costs, and time to infectious disease provider consult.[14]

Time to targeted therapy decreases when providers are notified of the RDT result as compared to reporting the final result after traditional identification many hours later.[15] Prompt notification to providers with RDT results has been successful through the use of a stewardship protocol. In these protocols, antibiotic stewardship practitioners evaluate the result, notify providers, and make recommendations for adjusting antimicrobial therapy as indicated.[14-17] Other studies have shown that without the implementation of a stewardship protocol for response, the benefits of RDT are not fully appreciated.[18-19] Although most published data regarding rapid PCR diagnostic testing are in adults, studies in the pediatric setting with real-time antimicrobial stewardship support have shown decreased time to optimal therapy. However, it is unknown if using GeneXpert in a pediatric institution in the absence of a formalized antimicrobial stewardship protocol to address the test results provides clinical benefit. Furthermore, few published data

describe the impact of PCR technology in children with SA bacteremia. The objective of this study was to determine the impact of GeneXpert technology on time to optimal therapy in pediatric patients with SA bacteremia at a single tertiary care pediatric institution without a formal antimicrobial stewardship intervention. We sought to test the hypothesis that GeneXpert testing in this population would be associated with decreased vancomycin usage.

Methods

This was a retrospective cohort study at a freestanding, 300-bed children's hospital. GeneXpert technology was implemented at the institution in January 2016. GeneXpert testing was utilized for blood cultures after Gram-positive cocci were observed in a smear of the culture broth and SA had been identified via rapid peptide nucleic acid fluorescence *in situ* hybridization (PNA-FISH). All laboratory services were performed in real-time. A medical laboratory scientist reported the PNA-FISH result to the medical team or nurse prior to detection of the mecA gene. If the isolate was SA, the results for the mecA testing were provided in the EMR upon completion of the GeneXpert test. Once the organism was isolated on solid media, definitive identification and antimicrobial susceptibility testing were performed per routine and reported in the medical record.

The institution had a formalized antimicrobial stewardship program during the studied time period, but lacked a specific protocol addressing dissemination of the GeneXpert result. Clinical pharmacists were responsible for antimicrobial stewardship on each medical service but there was no standardization; i.e. each pharmacist practiced their own individual approach.

Study Design and Population

The study included all patients with positive SA blood cultures at our institution during the study time period. Patients in the conventional group (pre-intervention group) had a positive blood culture from February 1, 2014 through March 31, 2015, and these blood cultures did not undergo GeneXpert testing. Patients in the GeneXpert group (post-implementation group) had a positive blood culture between February 1, 2016 and March 31, 2017, after GeneXpert technology was implemented for regular use. Only the first positive SA blood culture per study period per patient was included. Patients were excluded if they died before any culture results were available, if normal laboratory procedure for the specific time frame was not followed, or if result timing was not documented clearly in the electronic medical record (EMR). Patients were also excluded if no therapy was administered and/or the isolate was considered a contaminant, as documented in the EMR.

Optimal antimicrobial regimens were defined as vancomycin monotherapy for MRSA bacteremia and nafcillin, oxacillin, or cefazolin monotherapy for MSSA bacteremia. In patients where rifampin or clindamycin was added to the therapy listed above for synergistic purposes, therapy was still considered to be optimal for the purposes of this analysis. In patients with an absolute neutrophil count less than 500 cells/mm^3 during therapy, an anti-pseudomonal beta-lactam (piperacillin/tazobactam, cefepime, or meropenem) was considered optimal therapy for MSSA due to desired anti-pseudomonal activity in patients with febrile neutropenia. Adequate therapy was defined as any monotherapy or combination therapy where the specifically isolated organism was

within the spectrum of activity of the regimen, even if it was not the most narrow spectrum treatment.

Data including age, sex, hospital service, intensive care unit admission, antibiotic allergies, length of hospital stay, time to adequate and optimal therapy, and result of susceptibility testing were extracted from the medical record. Specific antimicrobial variables such as dose, frequency and duration were also collected.

The primary outcome was time to optimal therapy which was defined as the number of hours from collection of the blood samples to the initiation of an optimal regimen. Patient data were excluded from the primary outcome analysis if the blood culture exhibited polymicrobial growth (more than one pathogen grew from the same blood culture), or there was a secondary, concomitant infection with a non-SA pathogen at the time of culture collection. Vancomycin usage was assessed specifically in patients with monomicrobial MSSA bacteremia. Additional outcomes included time to adequate therapy, accuracy of GeneXpert output as compared to traditional bacterial identification determined based on matching result (methicillin susceptible or methicillin resistant), and length of hospital stay. The secondary outcome of length of stay was compared for the whole cohort, including patients with a polymicrobial blood culture. Vancomycin utilization was evaluated in patients with monomicrobial MSSA infections exclusively.

Statistical Analysis

Continuous data were described using mean and standard deviation (SD) for variables considered to be normally distributed and median and interquartile range (IQR) for non-normally distributed variables. Categorical variables were compared between groups using the Chi-square test or Fisher exact test. Continuous variables were

compared using the independent samples t-test or Mann-Whitney U test for non-parametric data. A p-value of 0.05 was considered to be statistically significant. Statistical analyses were conducted using Statistical Package for Social Sciences version 23.0 (SPSS v23.0). The study was approved by the institutional review board of the hospital.

Results

Overall, 110 patients had a positive SA blood culture during the study period and 101 patients were included (Figure 1). There were 61 patients in the conventional testing group, and 40 patients in the GeneXpert group.

There were no significant differences in gender, age, or weight between the conventional and GeneXpert cohorts (Table 1). In all GeneXpert group cases, the presence of the mecA gene, as determined by the RDT, was consistent with the identification and susceptibilities reported after completing conventional susceptibility testing.

The primary outcome was analyzed in 50 and 32 patients in the conventional testing and GeneXpert groups, respectively, after excluding polymicrobial cultures and patients with a secondary, concomitant infection. Median time [IQR] to optimal therapy from culture collection was decreased from 61.5 [47.8 – 68.1] hours in the conventional testing group to 42.5 [21.9 – 56.6] hours in the GeneXpert group ($p = 0.003$). Time to adequate therapy was 4.9 hours in the conventional testing group and 5 hours in the GeneXpert group ($p=0.658$) (Table 2).

Median [IQR] length of hospital stay was similar in the conventional testing group as compared to the GeneXpert group, 14.5 [9.3 - 48] days vs. 13 [6 – 60.5] days (p = 0.541).

Forty-two patients in the conventional testing group and 22 patients in the GeneXpert group had monomicrobial, MSSA-positive blood cultures. In this subset of the population, total hours of vancomycin therapy was 48.1 hours in the conventional testing group and 25.8 hours in the GeneXpert group (p = 0.009). Total doses of vancomycin given also decreased following implementation of GeneXpert (p = 0.014).

Discussion

In a previous study of blood cultures obtained from pediatric patients, GeneXpert was 100% sensitive and specific for MRSA and 100% sensitive and 99.5% specific for MSSA.[20] In our study, the GeneXpert result was concordant with the identification determined by traditional susceptibility testing in 100% of blood cultures.

Studies assessing clinical outcomes of rapid PCR testing in pediatric patient populations are limited. Veesenmeyer and colleagues compared traditional identification methods to the combination of peptide nucleic acid and PCR testing for identification and susceptibility in pediatric patients at a single children's hospital. Mean vancomycin duration utilization decreased in the total cohort from 53 hours with conventional testing to 35 hours in the rapid diagnostic testing group (p=0.01).[21] In patients infected with MSSA specifically, there was a decrease in the number of patients who received at least 24 hours of vancomycin therapy from 48% to 15% after implementation of rapid diagnostic testing, while mean hours of vancomycin therapy decreased from 30 hours to 9 hours (p=0.01).[21] In our MSSA patients specifically, there was a decrease in the number

of patients who received at least 24 hours of vancomycin therapy from 25% to 18.5% in our MSSA cohort. Total median hours of vancomycin therapy decreased by about 22 hours from the conventional testing group to the GeneXpert group, a similar margin of decreased hours of vancomycin therapy, despite not having comparable antimicrobial stewardship efforts. In our cohort, the total hours of vancomycin utilization is still much greater at 25.8 hours as compared to 9 hours. The effects of the GeneXpert may not be fully realized at our institution as there is no formalized protocol for response. The hospital studied by Veesenmeyer and colleagues has a well-established antimicrobial stewardship program which was active prior to and during the study. Unlike in our study, the antimicrobial stewardship pharmacist was paged with positive blood culture susceptibility results during the hours of 0700-1530, after which results were reviewed and recommendations were made.

In combination with antimicrobial stewardship program interventions in adults with SA bacteremia, rapid PCR testing decreases total hospital costs, pharmacy costs and time optimal antibiotic therapy.[14,19] In a study performed by Bauer and colleagues, the infectious disease clinical pharmacist was contacted with the PCR result and effective antibiotics were recommended to the team at that time. The mean LOS was 6.2 days shorter in the total population in patients with PCR testing ($p=0.07$) and a mean total hospital cost of $21,389 was saved ($p=0.02$). Carver and colleagues specifically assessed the importance of an antimicrobial stewardship intervention after mecA testing by comparing outcomes in a group with no formal intervention after mecA gene test results to the use of an infectious disease clinical pharmacist to provide clinical recommendations at the time of the mecA gene test result. In the group with immediate

infectious disease pharmacist intervention, time to optimal antibiotic therapy for patients with SA bacteremia was decreased from 64.7 hours to 39.3 hours.

In the pediatric population, Felsenstein addressed hospital cost in patients admitted to the general pediatric unit with SA bacteremia before and after implementation of a similar PCR rapid diagnostic test without a formal antimicrobial stewardship protocol and noted a non-significant median decrease of approximately $13,000.[22] Ray and colleagues looked at another PCR testing identification method, again with limited formal stewardship involvement and noted fourteen total bed days were saved with use of rapid PCR.[23] In our patient population, no difference in LOS was observed and cost was not assessed. Due to the complex nature of the patient population at our hospital, patients often had comorbidities keeping them in the hospital beyond resolution of the infection.

Limitations to this study exist in both methodology and analysis. Due to the sample size, we were unable to further analyze variability due to primary medical service, primary pharmacist, or primary physician. At our institution, patients can be medically complex and it was challenging to account for all of the potential factors which could impact a patient's antibiotic therapy. We tried to combat this by assessing whether patients had monomicrobial, polymicrobial, concomitant, or secondary infection. In doing so, we were able to exclusively analyze patients with a primary SA infection to capture de-escalation. Additionally, while we accounted for altered optimal therapy in febrile neutropenia patients, there was not a large enough sample of this patient population to analyze these patients individually. Information was not collected regarding the interventions made on weekdays as compared to weekends to assess the impact of

having rounding clinical pharmacists Monday through Friday. It is unknown how the time immediately following implementation, which was included in the post-intervention period, could have impacted the results. It is possible that as time went on and prescribers became more comfortable with the test, vancomycin exposure and time to therapy alteration decreased. This was not evaluated in the current study. Safety outcomes were not measured in this study, including potential adverse effects as a result of receiving vancomycin therapy.

Conclusions

In our pediatric population, the utilization of PCR testing to identify the presence of the mecA gene in SA blood cultures was associated with a decreased time to optimal therapy from culture collection. In patients with monomicrobial MSSA blood cultures, a significant difference in the total hours of vancomycin therapy was appreciated. Hospital length of stay in this cohort was not significantly impacted. It is unknown whether a formalized antimicrobial stewardship protocol for response would have a greater impact on these outcomes. Further studies are warranted to determine the impact of this rapid diagnostic testing method with varied antimicrobial stewardship responses in a variety of pediatric populations.

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Table 1: Baseline characteristics

	Conventional (n = 61)	GeneXpert (n = 40)	p-value
Male[a]	60.7 (37)	57.5 (23)	0.752
Age, years[b]	4.8 [0.4 – 10.8]	7.4 [0.3 – 14.1]	0.194
Weight, kg[b]	16.7 [5.3 – 37.6]	20.6 [5.3 – 46.4]	0.236

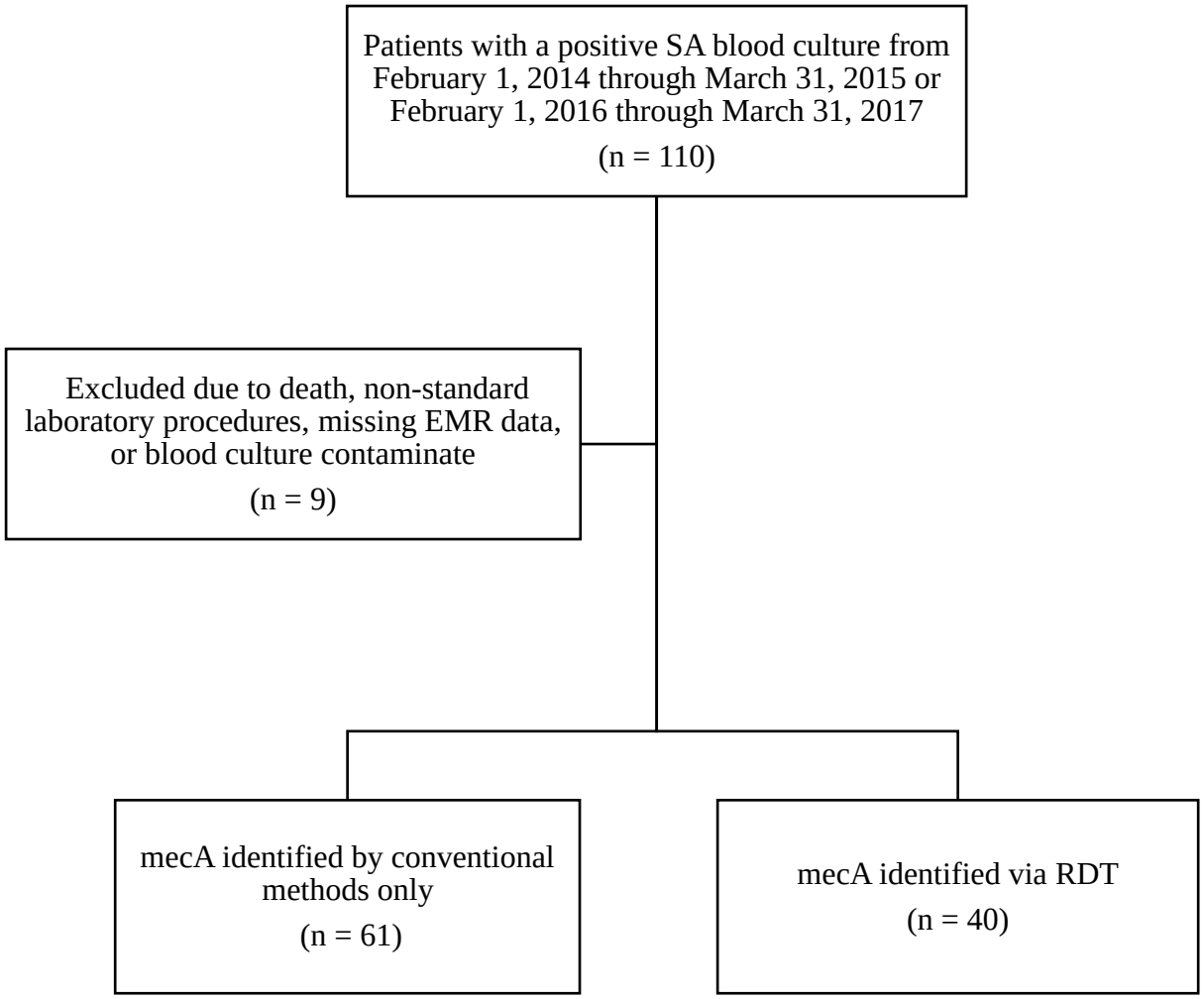
[a]data reported as % (n)
[b]data reported as median [IQR]

Table 2: Time to therapy

	Conventional (n = 50)	GeneXpert (n = 32)	p=value
Time to optimal therapy from culture collection, hours[a]	61.5 [47.8 – 68.1]	42.5 [21.9 – 56.6]	0.003
Time to optimal therapy from culture result, hours[a]	22.8 [-5.7 – 26.8]	2 [-22.6 – 25.7]	0.225
Time to adequate therapy from culture collection, hours[a]	4.9 [2.2 – 15.3]	5 [0.9 – 16.4]	0.658

[a]data reported as median [IQR]

Figure 1


Patients with a positive SA blood culture from February 1, 2014 through March 31, 2015 or February 1, 2016 through March 31, 2017
(n = 110)
Excluded due to death, non-standard laboratory procedures, missing EMR data, or blood culture contaminate
(n = 9)
mecA identified by conventional methods only
(n = 61)
mecA identified via RDT
(n = 40)