ORIGINAL ARTICLE

Assessment of Time to Clinical Response in Patients with Sepsis Treated Before and After Implementation of a Matrix-Assisted Laser Desorption Ionization Time-of-Flight Blood Culture Identification Algorithm

Joseph J. Carreno, PharmD;[1] Ben M. Lomaestro, PharmD;[2] Apryl L. Jacobs, PharmD;[1] Rachel E. Meyer, PharmD;[1] Ann Evans, BS;[3] Clemente I. Montero, PhD[3]

OBJECTIVE. To evaluate time to clinical response before and after implementation of rapid blood culture identification technologies.

DESIGN. Before-and-after trial.

SETTING. Large, tertiary, urban, academic health-sciences center.

PATIENTS. Patients >18 years old with sepsis and concurrent bacteremia or fungemia were included in the study; patients who were pregnant, had polymicrobial septicemia, or were transferred from an outside hospital were excluded.

INTERVENTION. Prior to the intervention, polymerase chain reaction was used to identify *Staphylococcus* species from positive blood cultures, and traditional laboratory techniques were used to identify non-staphylococcal species. After the intervention, matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) assay and FilmArray were also used to identify additional species. During both periods, the antimicrobial stewardship team provided prospective audit and feedback for all patients on antibiotics.

RESULTS. A total of 219 patients were enrolled in the study: 115 patients prior to the intervention and 104 after the intervention. The median time to clinical response was statistically significantly shorter in the postintervention group than in the preintervention group (2 days vs 4 days, respectively; $P = .002$). By Cox regression, the implementation of MALDI-TOF and FilmArray was associated with shorter time to clinical response (hazard ratio [HR], 1.360; 95% confidence interval [CI], 1.018–1.816). After controlling for potential confounders, the study group was not independently associated with clinical response (adjusted HR, 1.279; 95% CI, 0.955–1.713). Mortality was numerically, but not statistically significantly, lower in the postintervention group than in the preintervention group (7.6% vs 11.4%; $P = .342$).

CONCLUSIONS. In the setting of an existing antimicrobial stewardship program, implementation of MALDI-TOF and FilmArray was associated with improved time to clinical response. Further research is needed to fully describe the effect of antimicrobial stewardship programs on time to clinical response.

Infect Control Hosp Epidemiol 2016;37:916–923

Sepsis is a highly prevalent condition associated with significant morbidity and mortality worldwide.[1] Patients treated for sepsis have longer hospital lengths of stay, higher hospital costs, and higher risk of mortality than patients without sepsis.[2–4] In patients with sepsis complicated by bloodstream infections, prompt identification of bloodstream pathogens and timely initiation of appropriate antimicrobial therapy are 2 cornerstones of therapy.[5,6]

Antimicrobial stewardship programs (ASPs) have the potential to improve outcomes for patients with sepsis. ASPs have been shown to reduce time to pathogen identification and time to initiation of appropriate antimicrobial therapy.[5,7] With regard to pathogen identification, numerous rapid diagnostic assays (ie, polymerase chain reaction [PCR], matrix-assisted laser desorption ionization time of flight [MALDI-TOF], and FilmArray) have been used in ASPs to reduce time to pathogen identification.[8] In addition, when implemented within the context of real-time feedback, these assays have been associated with improved outcomes such as improved time to initiation of appropriate antimicrobial therapy, reduced hospital length of stay, reduced inpatient mortality, and reduced 30-day mortality.[9–13]

Affiliations: 1. Department of Pharmacy Practice, Albany College of Pharmacy and Health Sciences, Albany, New York; 2. Department of Pharmacy, Albany Medical Center Hospital Albany, New York; 3. Department of Microbiology, Albany Medical Center Hospital, Albany, New York.

PREVIOUS PRESENTATION. These data were presented in part in Abstract K-659 at the 54th Interscience Conference on Antimicrobial Agents and Chemotherapy in Washington, District of Columbia, on September 7, 2014.

Received December 11, 2015; accepted March 28, 2016; electronically published June 9, 2016

 0899-823X/2016/3708-0006. DOI: 10.1017/ice.2016.105

Despite these promising data, few studies have evaluated the impact of ASP on time to clinical response in patients with sepsis and concurrent bacteremia or fungemia. Time to clinical response is an important surrogate marker for patient outcomes because clinicians are unlikely to wait until the end of therapy to assess therapeutic failure. As such, early clinical response has been adopted in phase III clinical trials.[14,15] Recent analyses have suggested that time to clinical response may also serve as a proxy for discharge readiness.[15] However, it is unclear whether implementation of rapid diagnostics within ASPs has an impact on time to clinical response. Thus, the purpose of this study was to evaluate the effect of implementing rapid diagnostic technology in an organization with a preexisting ASP on the time to clinical response in patients with sepsis and concurrent bacteremia or fungemia.

METHODS

This study was a single-center, before-and-after study with 1 preintervention group and 1 postintervention group conducted at Albany Medical Center Hospital (AMCH); the institutional review board approved this study. Patients included were (1) >18 years old, (2) had at least 2 signs of systemic inflammatory response syndrome (SIRS), and (3) had concurrent bacteremia or fungemia. SIRS was composed of 4 mutually exclusive categories: (1) leukopenia (white blood cell count <4,000/cm^3), leukocytosis (white blood cell count >10,000/cm^3), or bandemia (>10% immature neutrophil forms); (2) tachycardia (heart rate >90 beats per minute); (3) tachypnea (respiratory rate >20 breaths per minute) or pCO_2 <32 mmHg; and (4) fever (temperature >38.0°C) or hypothermia (temperature <36.0°C). Patients were excluded if they (1) were transferred from an outside hospital with an active bloodstream infection, (2) had polymicrobial blood cultures, (3) had coagulase-negative staphylococci in blood cultures consistent with contamination, (4) were pregnant, or (5) had an absolute neutrophil count <1,000/mm^3.

Microbiology Workflow and Validation

The direct MALDI-TOF blood-culture identification method was approved for routine diagnostic testing at AMCH by the New York State Department of Health in October 2013. Identification using the MALDI-TOF Sepsityper Kit (Bruker Daltonics, Billerica, MA) was performed following manufacturer's recommendations using their blood-culture data settings. Scores were interpreted as follows: scores ≥1.8 genus- and species-level identification, score ≥1.6 to ≤1.79 genus-level identification. Scores ≤1.599 were considered unreliable and were not reported. No discrepant results affecting clinical management were observed in this study. The FilmArray blood culture panel (BCID; BioFire Diagnostics, Salt Lake City, UT) is a method for rapid identification approved by the Food and Drug Administration (FDA) that was validated prior to implementation in the postintervention group.

Preintervention: Initial Standard of Care

The first observational period was February 4, 2013, through August 31, 2013. During this time, all blood cultures were processed through the onsite microbiology laboratory at AMCH. This laboratory processed all blood samples in real time and identified blood-culture pathogens 24 hours per day, 7 days per week. During this study period, the primary method of pathogen identification and susceptibility testing used Sensititre (ThermoFisher Scientific, Waltham, MA). Gram-positive cocci in clusters (ie, *Staphylococcus* species) were identified using an in-house validated PCR-based assay implemented in 2005.[16] The antimicrobial stewardship team at AMCH consists of 3 rotating part-time infectious diseases physicians and 1 full-time infectious diseases pharmacist. During this study period, the antimicrobial stewardship team reviewed the antimicrobial regimens for each admitted patient and conducted walking rounds to provide prospective audit and feedback to clinicians once daily. In addition, a member of the antimicrobial stewardship team was available for consultation Monday through Friday between 9:00 AM and 3:30 PM.

Postintervention: MALDI-TOF and FilmArray Implementation

As the intervention in this study, the bloodstream pathogen identification algorithm was augmented to include additional technologies. The postintervention period was February 4, 2014 to August 31, 2014. MALDI-TOF Sepsityper identification was utilized for blood-culture pathogen identification between 4:00 AM and 3:00 PM and was performed on-demand for positive blood cultures. Between 3:00 PM and 4:00 AM FilmArray blood-culture identification panels were used to identify bacterial genus and species as well as specific resistance elements (ie, mecA, vanA, vanB, and KPC). The identification of *S. aureus* was conducted using the BacT/Alert automated blood-culture system (bioMèrieux, Marcy-l'Étoile, France), and the rapid identification was primarily performed using the assay developed in house. The results of these tests were reported in the electronic medical record with no specific notification to the clinicians. No other changes were made to the ASP during this period.

Outcomes

The primary endpoint was clinical response. Clinical response was defined as sustained reduction in baseline signs of systemic inflammatory response syndrome to <2 of the aforementioned SIRS categories for at least 24 hours. Secondary endpoints included (1) time from blood-culture collection to reporting of positive blood culture, (2) time from blood culture collection to reporting of final result, (3) time from blood culture collection to administration of initial systemic antimicrobial treatment, (4) time from blood culture collection to active antimicrobial therapy (ie, administration of first antibiotic with documented in vitro antimicrobial activity based on

https://doi.org/10.1017/ice.2016.105 Published online by Cambridge University Press

blood culture susceptibility report), (5) time to administration of final antimicrobial regimen, (6) hospital length of stay, (7) ICU length of stay, and (8) all-cause inpatient mortality.

Statistical Analysis

Baseline characteristics and continuous data were analyzed utilizing the Student *t* test for continuous parametric data and the Mann-Whitney U test for continuous nonparametric data. Categorical baseline characteristics and outcomes were analyzed using the χ^2 test for comparing proportions and Fisher's exact test for proportions with small sample sizes (ie, expected cell count <5). Time-to-event analyses were conducted using stratified Kaplan-Meier estimators (ie, the product limit method). Time to event was analyzed in days for clinical response and in minutes for antimicrobial administration. Time to clinical response was followed until death, discharge, or 30 days post blood culture. Survival distributions were compared with a log-rank test. Cox proportional hazards regression was used to determine the independent effect of the study group on clinical response. Multivariate logistic regression was used to determine the effect of the study group on inpatient mortality. For both multivariate analyses, all baseline variables associated with the outcome of interest ($P < .2$) and with prevalence at least 5% of the study population were considered as potential confounders. Variables were considered confounders if stepwise entry or removal into the models produced a >10% change in hazards or odds ratios for the Cox and logistic models, respectively. All calculations were computed using SPSS version 22.0 (SPSS, Chicago, IL).

RESULTS

A total of 219 patients (115 preintervention patients and 104 postintervention patients) were enrolled in the study. Baseline characteristics were comparable between groups (Table 1). In the preintervention group, the 2 most common techniques for pathogen identification were traditional methods and PCR. In the postintervention group, the combined rapid diagnostics algorithm resulted in a statistically significant decrease in the use of traditional methods with a concurrent increase in the use of PCR and MALDI-TOF ($P < .01$). Gram-positive organisms were the most commonly identified pathogens in the cultures and accounted for approximately 60% of all pathogens identified (Table 2).

Addition of the rapid diagnostic technology to the ASP was associated with improved clinical response (Figure 1). Overall, clinical response improved in the postintervention group (90.5% vs 80.7%; $P = .041$). Time to clinical response also improved in the postimplementation group. Median time to clinical response was 4 days (interquartile range [IQR],

TABLE 1. Baseline Characteristics

Characteristic	Preintervention (n = 114), No. (%)	Postintervention (n = 105) , No. (%)	*P* Value
Age, y (IQR)	61 (50–72)	63 (52–75)	.48
Male sex	79 (69.3)	73 (69.5)	.97
Race			
Caucasian	84 (73.7)	79 (75.2)	.47
African American	15 (13.2)	19 (18.1)	
Pacific Islander	2 (1.8)	1 (1.0)	
Hispanic	4 (3.5)	1 (1.0)	
Other	9 (7.9)	5 (4.8)	
Charlson score, median (IQR)	2 (0–3)	2 (0–3)	.17
SIRS at baseline, median (IQR)[a]	3 (2–3)	3 (2–3)	.05
Initially admitted to the ICU	36 (31.6)	30 (28.6)	.66
Infection site			
Genitourinary	28 (24.6)	20 (19.0)	.32
Lower respiratory tract	22 (19.3)	14 (13.3)	.23
Skin and soft tissue	15 (13.2)	13 (12.4)	.86
Endovascular	23 (20.2)	21 (20.0)	.97
Bone and joint	11 (9.6)	8 (7.6)	.59
Central nervous system	0 (0.0)	3 (2.9)	.11
Cardiovascular	9 (7.9)	13 (12.4)	.27
Ear, eyes, nose and throat	1 (0.9)	2 (1.9)	.61
Gastrointestinal	12 (10.5)	16 (15.2)	.30

NOTE. SIRS, systemic inflammatory response syndrome; ICU, intensive care unit; IQR, interquartile range. Sites are not mutually exclusive.

[a]SIRS was divided into 4 categories: (1) leukopenia, leukocytosis, or bandemia; (2) tachycardia; (3) tachypnea or pCO_2 <32 mmHg; and (4) fever or hypothermia. These data indicate the number of categories for which patients with SIRS were positive.

https://doi.org/10.1017/ice.2016.105 Published online by Cambridge University Press

TABLE 2. Pathogen Characteristics

Characteristic	Preintervention (n = 114), No. (%)[a]	Postintervention (n = 105), No. (%)[b]	*P* Value
Identification method			
Traditional	76 (66.7)	9 (8.6)	<.01
PCR	31 (27.2)	43 (41.0)	
MALDI-TOF	0 (0.0)	37 (35.2)	
Other	5 (4.4)	1 (1.0)	
Multiple methods used	2 (1.8)	15 (14.3)	
Identification reporting time			
Weekend	21 (18.4)	18 (17.1)	.81
Off hours[c]	63 (55.3)	49 (46.7)	.20
Weekend or off hours	77 (67.5)	61 (58.1)	.15
Gram-positive organism identified	68 (59.6)	67 (63.8)	.53
Staphylococcus aureus	32 (28.1)	35 (33.3)	.40
Methicillin-resistant	14 (12.3)	13 (12.4)	.98
Methicillin-susceptible	18 (15.8)	22 (21.0)	.32
Coagulase-negative *Staphylococcus*	4 (3.5)	12 (11.4)	.02
Streptococcus sp.	23 (20.2)	13 (12.4)	.12
Drug-resistant *S. pneumoniae*	3 (2.6)	3 (2.9)	1.00
Enterococcus spp.	7 (6.1)	5 (4.8)	.65
E. faecalis	4 (3.5)	4 (3.8)	1.00
E. faecium	3 (2.6)	1 (1.0)	.62
Vancomycin-resistant *Enterococcus* spp.	2 (1.8)	0 (0.0)	.50
Other Gram-positive organisms	2 (1.8)	2 (1.9)	1.00
Gram-negative organisms identified	46 (40.4)	37 (35.2)	.44
Escherichia coli	25 (21.9)	18 (17.1)	.37
Klebsiella sp.	8 (7.0)	7 (6.7)	.92
Enterobacter sp.	2 (1.8)	1 (1.0)	1.00
Pseudomonas aeruginosa	3 (2.6)	3 (2.9)	1.00
Acinetobacter spp.	1 (0.9)	0 (0.0)	1.00
Citrobacter spp.	0 (0.0)	4 (3.8)	.05
Multidrug-resistant Gram-negative organisms	18 (15.8)	16 (15.2)	1.00
Other Gram-negative organisms	7 (6.1)	4 (3.8)	.43
Yeast (*Candida* spp.)	0 (0.0)	1 (1.0)	.48

[a]In the preintervention group, traditional bacterial identification was performed using Sensititre and PCR was performed utilizing only the in-house assay developed for identification of *S. aureus*.
[b]In the postintervention group, PCR included the in-house assay developed for identification of *S. aureus* and FilmArray.
[c]Off hours: 3:30 PM to 9 AM.

2–6 days) in the preintervention group and 2 days (IQR, 1–4 days) in the postintervention group ($P = .002$). By Cox regression, the distribution of clinical response integrated over time improved in the postintervention group (hazard ratio [HR], 1.360; 95% confidence interval [CI], 1.018–1.816). However, the association between the study group and clinical response was not independently observed after adjusting for potential confounders (Table 3).

To further evaluate the effect of the antimicrobial stewardship team on clinical response, we conducted 2 subgroup analyses. For the first subgroup (group A), we evaluated sepsis resolution in patients for whom pathogen identification results had been reported during normal stewardship hours (ie, weekdays, 9:00 AM to 3:30 PM). For the second group (group B), we evaluated time to sepsis resolution in those patients who had pathogen identification results reported during off hours (ie, between 3:30 PM and 9:00 AM) or any time during the weekend. In group A (n = 81), overall sepsis resolution was numerically higher in the postintervention group than in the previntervention group (90.9% vs 83.8%; $P = .50$), and the median time to sepsis resolution was shorter in the postintervention group than in the preintervention group (2 days vs 4 days; $P = .41$). In group B (n = 138), overall sepsis resolution improved in the postimplementation group compared with the preintervention group (90% vs 79.2%; $P = .08$). Median time to sepsis resolution was somewhat shorter in the postintervention group than in the preintervention group (3 days vs 4 days; $P = .02$).

Process metrics related to the implementation of the algorithm were also examined (Figure 2). Time to Gram-stain

https://doi.org/10.1017/ice.2016.105 Published online by Cambridge University Press

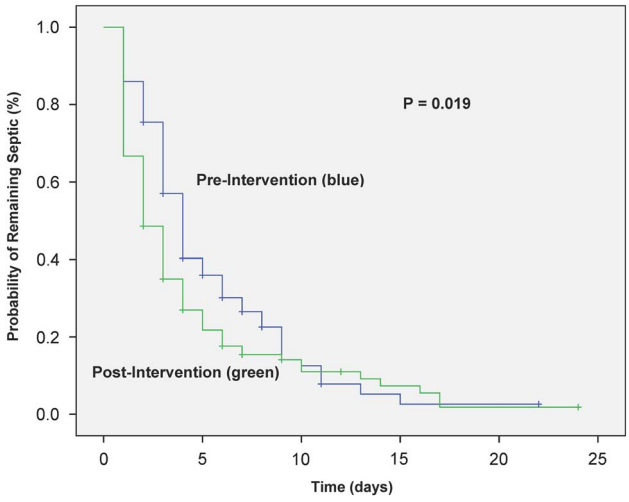

FIGURE 1. Time to clinical response. Clinical response was defined as sustained reduction in baseline signs of systemic inflammatory response syndrome to <2 SIRS categories for at least 24 hours. Time-to-event analyses were conducted utilizing stratified Kaplan-Meier estimators (ie, the product limit method). Time to event was analyzed in days for clinical response and time points were followed until death, discharge, or 30 days after blood culture. Survival distributions were compared using the log-rank test.

TABLE 3. Factors Associated with Clinical Response

Variable[a]	aHR (95% CI)	*P* Value[b]
Study group	1.279 (0.955–1.713)	.099
CoNS identified	2.053 (1.258–3.352)	.004
Lower respiratory tract infection	0.522 (0.330–0.825)	.005
MRSA identified	0.684 (0.436–1.075)	.099

NOTE. aHR, adjusted hazard ratio.

[a]Initial variables considered for inclusion included initially admitted to the intensive care unit, methicillin-resistant *Staphylococcus aureus*, methicillin-sensitive *Staphylococcus aureus*, methicillin-resistant coagulase-negative staphylococci, other Gram-negative organisms, study group, lower respiratory tract infection, skin and soft tissue infection, glycemic index, and age.

[b]*P* values were obtained by Cox regression.

reporting was unchanged between study periods. However, the combined identification algorithm resulted in decreased time to pathogen identification. Time-to-susceptibility reporting was unchanged. In the postintervention group, time to initial therapy was statistically significantly shorter than in the preintervention group (0.06 days vs 0.18 days; $P < .001$), and time to first active dose was also statistically significantly shorter than in the preintervention group (0.13 days vs 0.29 days; $P = .015$); however, no other treatment-related outcomes changed (Table 4). Median hospital length of stay was unchanged between study groups (9 days vs 10 days in pre-intervention and post-intervention groups, respectively; $P = .249$).

Mortality was also examined as a secondary endpoint. In the bivariate comparison, incidence of mortality was numerically lower in the postintervention study interval than in the preintervention interval (7.6% vs 11.4%; $P = .342$). In the multivariate logistic regression model, the postintervention group was associated with a nonsignificant decrease in the odds of mortality (adjusted odds ratio [aOR], 0.56; 95% CI, 0.27–2.03). Factors determined to be independently associated with mortality included presence of a multidrug-resistant pathogen, lower respiratory tract infection, endovascular infection, and time (in days) to final regimen (Table 5).

DISCUSSION

Our study has demonstrated that, in the setting of a preexisting ASP, implementation of this rapid diagnostic algorithm was associated with improvement in time to clinical response. To our knowledge, this is one of the first studies to evaluate the effect of rapid diagnostics with antimicrobial stewardship on time to clinical response. To date, few studies have evaluated clinical response as a function of time.[14] Recently, however, the FDA has incorporated time to clinical response into guidance for conducting phase III clinical trials.[17,18] In the updated guidance, the FDA now suggests evaluation of early clinical response in phase III clinical trials for acute bacterial skin and skin structure infection and for community-acquired bacterial pneumonia. Accordingly, we evaluated the effect of an antimicrobial stewardship intervention on time to clinical response.

Another unique aspect of this study was that we did not use real-time notification or feedback. Instead, members of the antimicrobial stewardship team performed once-daily antimicrobial stewardship rounds of all patients on antibiotics. Previous studies evaluating the impact of rapid diagnostics have suggested that implementation of rapid diagnostics without real-time reporting to and real-time feedback from an antimicrobial stewardship team has little or no impact on patient outcomes.[19–22] In contrast, we have demonstrated the benefit of implementing this new rapid identification technology with once-daily antimicrobial stewardship rounds. This finding is important because many institutions may be hesitant to adopt these technologies due to limited ASP resources.[23]

The implementation of once-daily antimicrobial stewardship rounds has the potential to be advantageous in hospitals with limited staffing for several reasons. Numerous studies have suggested that antimicrobial de-escalation is the most common stewardship intervention following implementation of rapid diagnostic technology.[9–12] One of the major benefits of de-escalation is the reduction of hospital costs directly through reduced antimicrobial use. The implementation of once-daily antimicrobial stewardship rounds can produce similar costs savings for once-daily antibiotics because discontinuation of a once daily drug at any point during the dosing interval will produce a net reduction in 1 dose. For drugs administered multiple times per day, there is a net loss equal to the number of daily doses minus one. However,

https://doi.org/10.1017/ice.2016.105 Published online by Cambridge University Press

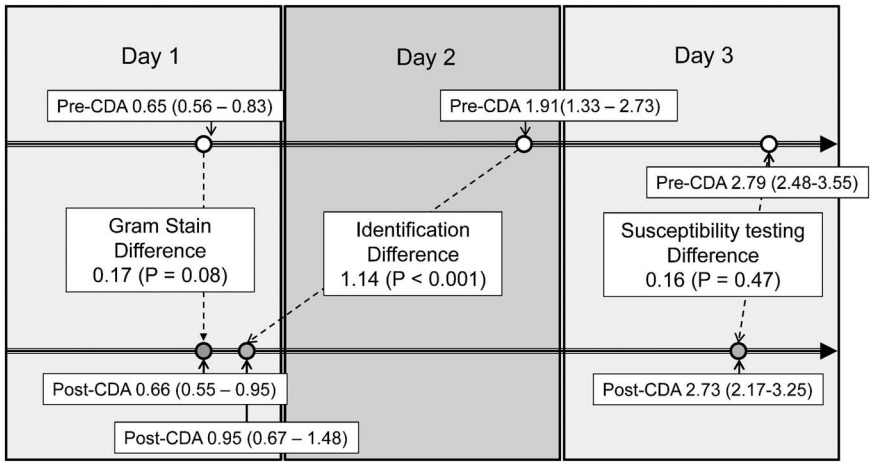

FIGURE 2. Implementation of combined diagnostic algorithm (CDA). Data are means (95% CI). *P* value was obtained from a Mann-Whitney U test.

TABLE 4. Secondary Outcomes

	Preintervention (n = 115)	Postintervention (n = 104)	*P* Value[a]
Treatment-related outcomes, median (IQR)			
Time to initial therapy	0.18 (0.04–0.50)	0.06 (0.01–0.17)	<.001
Time to active therapy	0.30 (0.06–0.87)	0.12 (0.04–0.68)	.015
Time to final regimen	2.20 (0.81–4.47)	2.40 (1.02–4.03)	.786
Clinical outcomes, No. (%)			
Inpatient mortality	13 (11.4)	8 (7.6)	.342
Hospital length of stay	9 (4–15)	10 (6–16)	.249
ICU length of stay (n = 86)	4 (2–7)	5 (2–8)	.363

NOTE. IQR, interquartile range; ICU, intensive care unit. Time in Days.
[a]P values were obtained using the Mann-Whitney U test, χ^2 test, or Fisher's exact test.

TABLE 5. Factors Associated with Inpatient Mortality

	aOR (95% CI)	*P* Value
Study group	0.74 (0.27–2.03)	.56
Multidrug-resistant organism identified	2.77 (1.00–7.667)	.05
Lower respiratory tract infection	6.80 (1.90–24.30)	<.01
Endovascular infection	4.50 (1.24–16.34)	.02
Time to final regimen	1.11 (1.04–1.18)	<.01

NOTE. Initial variables considered for inclusion included, multidrug-resistant organisms identified: methicillin-resistant *Staphylococcus aureus* (MRSA), drug-resistant *S. pneumonia* (DRSP), vancomycin-resistant Enterococci (VRE), multidrug-resistant Gram-negative bacilli (MDRGNB), age, sex, initially admitted to the ICU, Charlson score, lower respiratory tract infection, endovascular infection, time to first antibiotic dose, time to first active antibiotic dose, time to final regimen; time in days.

depending on the frequency and costs of the antibiotics used, the cost of these extra doses may not exceed the full-time equivalents needed for real-time feedback. Hence, a once-daily antimicrobial stewardship approach may be appealing to hospitals with fewer staffing resources. Unfortunately, the theoretical decrease in antimicrobial expenditures and increase in antimicrobial utilization was beyond the scope of the present study. In addition to cost comparison, comparative data between once-daily and real-time feedback would be useful for evaluating this type of intervention.

In our study, reduction in hospital length of stay was not observed. This finding is consistent with other literature evaluating similar patient populations. Comparable to our study, Huang et al[11] did not observe a significant reduction in length of stay after the implementation of MALDI-TOF (14 days preintervention vs 11 days postintervention; $P = .066$). The length of stay observed by Huang et al is also analogous to our length of stay findings (9 days preintervention vs 10 days postintervention; $P = .249$). In contrast to our findings, Perez et al[13] observed a significant reduction in length of stay after implementation of MALDI-TOF (23.3 days preintervention vs 15.3 days postintervention; $P = .0001$). We believe that the difference in this finding is due to differences in baseline pathogens.

Mortality was not statistically significantly reduced in our study (11.4% preintervention vs 7.6% postintervention; $P = .34$). Perez et al[13] also examined in-hospital mortality after the implementation of MALDI-TOF technology within an

https://doi.org/10.1017/ice.2016.105 Published online by Cambridge University Press

ASP. In their study, mortality was reduced from 21% preintervention to 8.9% postintervention ($P = .01$). However, their study included a cohort of patients with antibiotic-resistant Gram-negative bacteremia. In the preintervention group, the authors note that a lack of rapid identification of resistance elements may have caused delays in time to appropriate therapy (mean time to active antibiotic therapy, 89.7 hours). Consistent with the literature,[6] delays in time to active antimicrobial therapy were associated with mortality risk.[13] In contrast, our mean time to active antibiotic therapy in our preintervention group was 7.20 hours. The shorter time to active antimicrobial therapy in our study may have accounted for differences in baseline mortality between our study and previous investigations. Because our baseline mortality was lower than that observed by Perez et al, we may have experienced diminished returns compared with a population with a higher mortality risk.[24]

We are aware of several limitations of this study. As with any quasi-experimental study, temporal trends can affect study results. The 2 main temporal trends which may have affected this data were the "July effect"[25] and the individual effect of implementing a novel rapid diagnostic without an ASP. The July effect refers to the theoretically decreased quality of inpatient care due to the changeovers that occurred at the beginning of a new academic year.[25] To limit the impact of the "July Effect" on this study, we evaluated 2 groups during the same months in 2 different study years. Thus, any July effect would affect both groups equally. The effect of implementing a rapid diagnostic technology without an ASP has been well documented.[19–22] In settings with no ASP, implementation of a rapid diagnostic technology does not improve patient outcomes. Therefore, any changes in time to clinical response that we observed are likely due to the combination of the rapid diagnostic technology with once-daily antimicrobial stewardship rounds.

As with any retrospective observational study, confounding can affect the interpretation of the study results.[24,26] In our study, we observed an equitable distribution of baseline infection types and pathogens. For those disease states and pathogens with unequal distributions and adequate sample size, the impact of disease state and pathogen was assessed for the effect on clinical response. In the final model for clinical response, coagulase-negative staphylococci and lower respiratory tract infection were associated with probability of response. These findings are not surprising considering that coagulase-negative staphylococci have limited virulence factors and that pneumonia is still among the most common causes of prolonged hospitalization. However, these findings highlight the interplay between disease severity and clinical response. As such, these observations suggest that patients with more severe illness have prolonged time to clinical response.

Our results have numerous implications. This study is among the first to demonstrate the impact of an ASP on time to clinical response. Time to clinical response is an important outcome that has previously been associated with several important long-term outcomes.[27–29] In addition, we have proposed an efficient, low-resource method by which ASPs can implement rapid diagnostics within their health system. Lack of funding and/or personnel are often cited as barriers to functional and effective ASPs.[23] Our data suggest that combining rapid diagnostic technology with once-daily antimicrobial stewardship rounds can improve patient outcomes. Use of multiple technologies (ie, PCR, MALDI-TOF, and FilmArray) may also be efficient for the microbiology laboratory. FilmArray requires less "hands on" time than MALDI-TOF or other PCR methods; therefore, using FilmArray as an off-hours technology may be advantageous because it requires less staffing. As ASPs move toward implementing rapid diagnostic technologies, programs may consider once-daily antimicrobial stewardship rounds as an effective and efficient alternative model. However, comparative evaluations of once-daily versus multiple daily interventions are needed prior to widespread adoption of once-daily antimicrobial stewardship rounds in the context of rapid diagnostics.

In conclusion, time to clinical response was improved in patients with sepsis and concurrent bacteremia or fungemia after implementation of rapid diagnostic technologies within an existing ASP. This model may be of interest to administrators of health systems seeking to implement rapid diagnostic technology in settings with limited funding for staffing. Further research is required to determine the effect on time to sepsis resolution on long-term patient outcomes.

ACKNOWLEDGMENTS

The authors acknowledge Nicole Bilan, Stephen Bradley, Mara Garfinkel, Joseph Gervasio, Christopher Hunter, Lindsay Itro, Katherine Lyndaker, and Tori Smiraglia for their assistance with data collection. In addition, the authors acknowledge Kathleen Stellrecht and the molecular microbiology team for the development or implementation of the PCR based tools used in this study.

Financial support: J.J.C. received grant support from Albany College of Pharmacy and Health Sciences.

Potential conflicts of interest: J.J.C. reports that he has been a speaker for Cubist Pharmaceuticals, a wholly owned subsidiary of Merck and Company. All other authors report no conflicts of interest relevant to this article.

Address correspondence to Joseph J. Carreno, PharmD, Albany College of Pharmacy and Health Sciences, School of Pharmacy and Pharmaceutical Sciences, Department of Pharmacy Practice, Albany, NY, 12208 (Joseph.Carreno@acphs.edu).

REFERENCES

1. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. *Virulence* 2014;5:4–11.
2. Hall MJ, Williams SN, DeFrances CJ, Golosinskiy A. Inpatient care for septicemia or sepsis: a challenge for patients and hospitals. *NCHS Data Brief* 2011:1–8.
3. McPherson D, Griffiths C, Williams M, et al. Sepsis-associated mortality in England: an analysis of multiple cause of death data from 2001 to 2010. *BMJ Open* 2013;3.
4. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among

https://doi.org/10.1017/ice.2016.105 Published online by Cambridge University Press

critically ill patients in Australia and New Zealand, 2000–2012. *JAMA* 2014;311:1308–1316.
5. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013;39: 165–228.
6. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006;34:1589–1596.
7. Dellit TH, Owens RC, McGowan JE, Jr., et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007;44: 159–177.
8. Bauer KA, Perez KK, Forrest GN, Goff DA. Review of rapid diagnostic tests used by antimicrobial stewardship programs. *Clin Infect Dis* 2014;59(Suppl 3):S134–S145.
9. Bauer KA, West JE, Balada-Llasat JM, Pancholi P, Stevenson KB, Goff DA. An antimicrobial stewardship program's impact with rapid polymerase chain reaction methicillin-resistant *Staphylococcus aureus/S. aureus* blood culture test in patients with S. aureus bacteremia. *Clin Infect Dis* 2010;51:1074–1080.
10. Wong JR, Bauer KA, Mangino JE, Goff DA. Antimicrobial stewardship pharmacist interventions for coagulase-negative staphylococci positive blood cultures using rapid polymerase chain reaction. *Annals Pharmacotherapy* 2012;46:1484–1490.
11. Huang AM, Newton D, Kunapuli A, et al. Impact of rapid organism identification via matrix-assisted laser desorption/ ionization time-of-flight combined with antimicrobial stewardship team intervention in adult patients with bacteremia and candidemia. *Clin Infect Dis* 2013;57:1237–1245.
12. Nagel JL, Huang AM, Kunapuli A, et al. Impact of antimicrobial stewardship intervention on coagulase-negative *Staphylococcus* blood cultures in conjunction with rapid diagnostic testing. *J Clin Microbiol* 2014;52:2849–2854.
13. Perez KK, Olsen RJ, Musick WL, et al. Integrating rapid diagnostics and antimicrobial stewardship improves outcomes in patients with antibiotic-resistant Gram-negative bacteremia. *J Infect* 2014;69:216–225.
14. Powers JH. Increasing the efficiency of clinical trials of antimicrobials: the scientific basis of substantial evidence of effectiveness of drugs. *Clin Infect Dis* 2007;45(Suppl 2):S153–S162.
15. Lodise TP, Anzueto AR, Weber DJ, et al. Assessment of time to clinical response, a proxy for discharge readiness, among hospitalized patients with community-acquired pneumonia who received either ceftaroline fosamil or ceftriaxone in two phase III FOCUS trials. *Antimicrob Agent Chemother* 2015;59: 1119–1126.
16. Stellrecht KA, Grifasi ML, Graffunder EM, Lodise TP. Impact of rapid PCR blood culture testing for *Staphylococcus aureus* and MRSA on patient care. 49th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2009; Chicago, IL.
17. Antimicrobial Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment. Food and Drug Administration website. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234907.pdf. Published 2010. Accessed August 25, 2011.
18. Guidance for Industry. Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment, Draft Guidance. Food and Drug Administration website. http://www.fda.gov.elibrary.amc.edu/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm123686.pdf. Published 2009. Accessed August 8, 2014.
19. Frye AM, Baker CA, Rustvold DL, et al. Clinical impact of a real-time PCR assay for rapid identification of staphylococcal bacteremia. *J Clin Microbiol* 2012;50:127–133.
20. Terp S, Krishnadasan A, Bowen W, et al. Introduction of rapid methicillin-resistant *Staphylococcus aureus* polymerase chain reaction testing and antibiotic selection among hospitalized patients with purulent skin infections. *Clin Infect Dis* 2014;58:e129–e132.
21. Ly T, Gulia J, Pyrgos V, Waga M, Shoham S. Impact upon clinical outcomes of translation of PNA FISH-generated laboratory data from the clinical microbiology bench to bedside in real time. *Ther Clin Risk Manag* 2008;4:637–640.
22. Holtzman C, Whitney D, Barlam T, Miller NS. Assessment of impact of peptide nucleic acid fluorescence in situ hybridization for rapid identification of coagulase-negative staphylococci in the absence of antimicrobial stewardship intervention. *J Clin Microbiol* 2011;49:1581–1582.
23. Johannsson B, Beekmann SE, Srinivasan A, Hersh AL, Laxminarayan R, Polgreen PM. Improving antimicrobial stewardship: the evolution of programmatic strategies and barriers. *Infect Control Hosp Epidemiol* 2011;32:367–374.
24. Harris AD, Bradham DD, Baumgarten M, Zuckerman IH, Fink JC, Perencevich EN. The use and interpretation of quasi-experimental studies in infectious diseases. *Clin Infect Dis* 2004;38:1586–1591.
25. Young JQ, Ranji SR, Wachter RM, Lee CM, Niehaus B, Auerbach AD. "July effect": impact of the academic year-end changeover on patient outcomes: a systematic review. *Annals Internal Med* 2011;155:309–315.
26. Shardell M, Harris AD, El-Kamary SS, Furuno JP, Miller RR, Perencevich EN. Statistical analysis and application of quasi experiments to antimicrobial resistance intervention studies. *Clin Infect Dis* 2007;45:901–907.
27. Zasowski E, Butterfield JM, McNutt LA, et al. Relationship between time to clinical response and outcomes among Pneumonia Outcomes Research Team (PORT) risk class III and IV hospitalized patients with community-acquired pneumonia who received ceftriaxone and azithromycin. *Antimicrob Agent Chemother* 2014;58:3804–3813.
28. Halm EA, Fine MJ, Marrie TJ, et al. Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. *JAMA* 1998;279:1452–1457.
29. Aliberti S, Peyrani P, Filardo G, et al. Association between time to clinical stability and outcomes after discharge in hospitalized patients with community-acquired pneumonia. *Chest* 2011;140: 482–488.