MAJOR ARTICLE

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

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Background. Integration of rapid diagnostic testing via matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) with antimicrobial stewardship team (AST) intervention has the potential for early organism identification, customization of antibiotic therapy, and improvement in patient outcomes. The objective of this study was to assess the impact of this combined approach on clinical and antimicrobial therapy–related outcomes in patients with bloodstream infections.

Methods. A pre–post quasi-experimental study was conducted to analyze the impact of MALDI-TOF with AST intervention in patients with bloodstream infections. The AST provided evidence-based antibiotic recommendations after receiving real-time notification following blood culture Gram stain, organism identification, and antimicrobial susceptibilities. Outcomes were compared to a historic control group.

Results. A total of 501 patients with bacteremia or candidemia were included in the final analysis: 245 patients in the intervention group and 256 patients in the preintervention group. MALDI-TOF with AST intervention decreased time to organism identification (84.0 vs 55.9 hours, $P < .001$), and improved time to effective antibiotic therapy (30.1 vs 20.4 hours, $P = .021$) and optimal antibiotic therapy (90.3 vs 47.3 hours, $P < .001$). Mortality (20.3% vs 14.5%), length of intensive care unit stay (14.9 vs 8.3 days) and recurrent bacteremia (5.9% vs 2.0%) were lower in the intervention group on univariate analysis, and acceptance of an AST intervention was associated with a trend toward reduced mortality on multivariable analysis (odds ratio, 0.55, $P = .075$).

Conclusion. MALDI-TOF with AST intervention decreased time to organism identification and time to effective and optimal antibiotic therapy.

Keywords. MALDI-TOF; antimicrobial stewardship; bacteremia; candidemia.

Bloodstream infections (BSIs) are associated with high rates of morbidity and mortality among hospitalized patients despite advances in antimicrobial therapy and supportive care [1].

Prompt pathogen identification is crucial for optimizing antimicrobial therapy in patients with BSIs, and timely initiation of appropriate antibiotics is associated with improved patient outcomes and decreased healthcare expenditures [2–7]. Delays in microbiological identification hinder the ability of clinicians to streamline therapy, resulting in excessive patient exposure to broad-spectrum antimicrobials and subsequent risk of isolates developing antibiotic resistance [8].

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Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) utilizes mass spectrometry to rapidly identify organisms following isolation from clinical specimens. MALDI-TOF accurately and promptly identifies most bacterial and yeast species and represents an attractive alternative to more time-consuming conventional testing methods [9, 10]. Integration of MALDI-TOF into clinical microbiology workflow decreases time to organism identification by 1.2–1.5 days compared to conventional methods [6, 11, 12]. However, there are limited data evaluating the impact of MALDI-TOF implementation on patient outcomes [6]. Furthermore, previous studies demonstrate that antimicrobial stewardship teams (ASTs) that provide real-time review and intervention improve patient outcomes compared to reporting of microbiology results alone [13–15]. Therefore, the aim of this study was to evaluate the impact of rapid pathogen identification with MALDI-TOF combined with AST intervention on clinical and antimicrobial therapy–related outcomes in patients with BSIs.

METHODS

Study Design

This single-center, pre–post quasi-experimental study was conducted at the University of Michigan Hospitals and Health System and received institutional review board approval. Adult patients >18 years of age with a BSI identified via MALDI-TOF over a 3-month period (1 September–30 November 2012) were compared to a historical control group with organism identification performed by conventional methods over the same 3 calendar months in the previous year (1 September 2011–30 November 2011). Patients transferred from an outside hospital with an active BSI were excluded. Additionally, patients with a BSI secondary to organisms not validated for identification by MALDI-TOF at the time of this study that required identification by other methods were excluded in both groups. Organisms excluded include *Mycobacterium* species, *Nocardia* species, anaerobic organisms, and filamentous fungi.

Microbiology Workflow and MALDI-TOF Validation

Blood cultures were performed using FAN media on the BacT/Alert system (bioMérieux, Durham, North Carolina). Aliquots from bottles that signaled positive were Gram stained and subcultured, and results of the Gram stain were communicated directly to the ordering clinicians during both study periods. Results were posted to the clinical information system once verbal notification was performed. Organism identification and antimicrobial susceptibility testing results were routinely reported between 6:00 AM and 11:30 PM during both the intervention and control periods. Organism susceptibilities were tested with VITEK-2, Etest (bioMérieux, Durham, North Carolina), disk diffusion (Becton Dickinson, Sparks, Maryland), or broth microdilution (TREK Diagnostic Systems, Cleveland, Ohio) and did not differ between study periods.

Prior to the initiation of the study, we verified the performance of MALDI-TOF for identification by evaluating an extensive array of aerobic gram-positive (n = 222), aerobic gram-negative (n = 218), and yeast (n = 201) isolates. The percentage of agreement between MALDI-TOF and conventional identification was 98.6% for gram-positive isolates, 98.2% for gram-negative isolates, 98.5% for yeast, and 98.4% for isolates tested overall.

During the intervention period, isolates recovered from positive blood cultures were identified by MALDI-TOF mass spectrometry using the Bruker Microflex instrument, Biotyper software version 3.0, and database version 3.1.0 (Bruker Daltonik, Bremen, Germany). Positive blood cultures were subcultured to solid media and incubated overnight. Isolates were processed by either direct transfer (with or without formic acid overlay), or manual formic acid extraction procedures as recommended by the manufacturer, and Biotyper scores were interpreted as previously reported [11, 16] (but are briefly described below). All isolates were initially spotted in duplicate onto the manufacturer's reusable steel target plates, with gram-negative isolates testing following the addition of matrix. Gram-positive and yeast isolates were tested following the addition of matrix and formic acid overlays. Species-level identifications were accepted if the following criteria were met: paired results yielded the same identification, Biotyper scores were $\geq$2.0 for bacteria or $\geq$1.7 for yeast, and the next closest identification generated a Biotyper score >10% different than the top score [11, 16]. Isolates that did not achieve acceptable initial scores were retested in duplicate following manual formic acid extraction.

MALDI-TOF With Stewardship Intervention Study Period

The AST at the University of Michigan Hospitals consists of 2 infectious diseases physicians, 3 infectious diseases pharmacists, and an infectious diseases pharmacy resident. An AST member received real-time notification for all patients with positive blood cultures with bacteria and yeast and provided prescribers with preestablished, evidence-based antibiotic recommendations in accordance with institutional guidelines at the time of Gram stain, organism identification, and antimicrobial susceptibility testing results. The AST utilized clinical decision support computer software (TheraDoc Version 4.4, Hospira, Lake Forest, Illinois) to receive real-time electronic pages between 6:00 AM and 11:30 PM. These real-time alerts allowed for AST review of pertinent electronic medical records and intervention at the time of all organism identification, reporting of susceptibility results, and the majority of Gram stain results. In addition to real-time pages, AST members also received email notification 24 hours a day. Gram stain results

reported between 11:30 PM and 6:00 AM were reviewed the following morning.

Preintervention Study Period

During the control period, organism identification was performed via conventional methods, primarily utilizing VITEK-2 (bioMérieux). Prescribers were immediately notified of positive Gram stain results from blood cultures. The AST did not intervene on positive bacterial cultures in real time during this time period, except for patients with yeast on Gram stain. AST members recommended timely initiation of antifungal therapy Monday through Friday from 7:00 AM to 5:00 PM as part of a comprehensive bundle to promote appropriate management of patients with candidemia [17]. The AST also reviewed daily reports Monday through Friday of all patients receiving restricted antimicrobials (carbapenems, daptomycin, linezolid, quinupristin/dalfopristin, ceftaroline, voriconazole, posaconazole, and liposomal amphotericin B) and recommended therapy changes based on institutional guidelines and clinical judgment when appropriate. All stewardship activities, except for the addition of real-time alerts for positive blood cultures during the intervention period, remained unchanged during the study time frame.

Outcomes

The study objective was to analyze clinical outcomes following initiation of rapid organism identification via MALDI-TOF in combination with AST intervention, including 30-day all-cause mortality, hospital and intensive care unit (ICU) length of stay following blood culture positivity, microbiologic clearance, recurrent bacteremia within 30 days of discontinuation of antimicrobial therapy, and 30-day readmission for recurrent bacteremia with the same organism. Microbiological clearance was defined by the first negative blood culture result.

Additionally, time to effective and time to optimal antimicrobial therapy were measured. Time to effective therapy was defined as the time from blood culture draw to the time of administration of the first antimicrobial with known susceptibility per microbiology report. Time to optimal therapy was defined as time from blood culture draw to the time the patient received appropriate antibiotic therapy, which included de-escalation based on known susceptibility results, need to cover other polymicrobial infection, concomitant infections, antibiotic allergies or intolerances, discontinuation of antimicrobials if pathogen in blood culture was determined to be a contaminant, and discontinuation of unnecessary antibiotic coverage targeting other organisms (eg, discontinuation of gram-negative therapy for a patient with *Staphylococcus aureus* bacteremia). Time to optimal therapy for any patient with a pathogen or combination of infections that did not fall within evidence-based guidelines was adjudicated by an infectious diseases physician.

Patients with a positive blood culture with coagulase-negative *Staphylococcus* and other skin flora determined to be a contaminant were excluded from clinical outcomes analysis. Patients with coagulase-negative *Staphylococcus* recovered from one set of cultures when 2 or more blood culture sets were collected were deemed a contaminant, except for patients with suspected infection of central venous catheters, or surgically implanted prosthetic material, device, or hardware.

The AST recorded all recommended interventions and prescriber acceptance rate, as well as timing of the intervention in relation to Gram stain, organism identification, and antimicrobial susceptibilities during the intervention period. Interventions were classified as broadening or initiating coverage, narrowing antimicrobial coverage to target the isolated organism, discontinuing therapy targeting organisms not isolated, or other.

Statistical Analysis

All statistical analyses were performed using SPSS software, version 20.0 (SPSS, Inc, Chicago, Illinois). Demographic data were analyzed by descriptive statistics, outcomes with categorical data were analyzed by 2-tailed Student *t* test, and dichotomous data were analyzed by Pearson χ^2 test. Overall survival was analyzed by the Kaplan-Meier method with use of 2-sided log-rank statistics. A stratified analysis was conducted to evaluate clinical outcomes for patients with gram-positive organisms, gram-negative organisms, and yeast. Unconditional logistic regression analysis was performed to evaluate for factors associated with mortality including the following covariates: source of infection, comorbidities, type of organism (gram-positive, gram-negative, yeast), ICU status at the time of BSI, MALDI-TOF with accepted AST intervention, age, and immunosuppression. Factors with a P value of $\leq .20$ on the bivariate model were included in a multivariate logistic regression analysis. In the final model, $P \leq .05$ (2-tailed) was considered statistically significant.

RESULTS

A total of 908 patients with positive blood cultures were identified during both study periods, and 501 were included in the final analysis. The preintervention group and intervention group included 256 and 245 patients, respectively (Figure 1). Demographic characteristics including comorbidities, clinical status at the time of BSI, setting of acquisition (healthcare associated, community acquired, or hospital acquired), and source of BSI were similar in both groups (Table 1). Patients in the preintervention group were slightly older (59.5 vs 56.5 years, $P = .030$), and more patients in the intervention group received chemotherapy within 90 days prior to BSI (14.5% vs 21.6%, $P = .047$); however, the rate of neutropenia was similar between

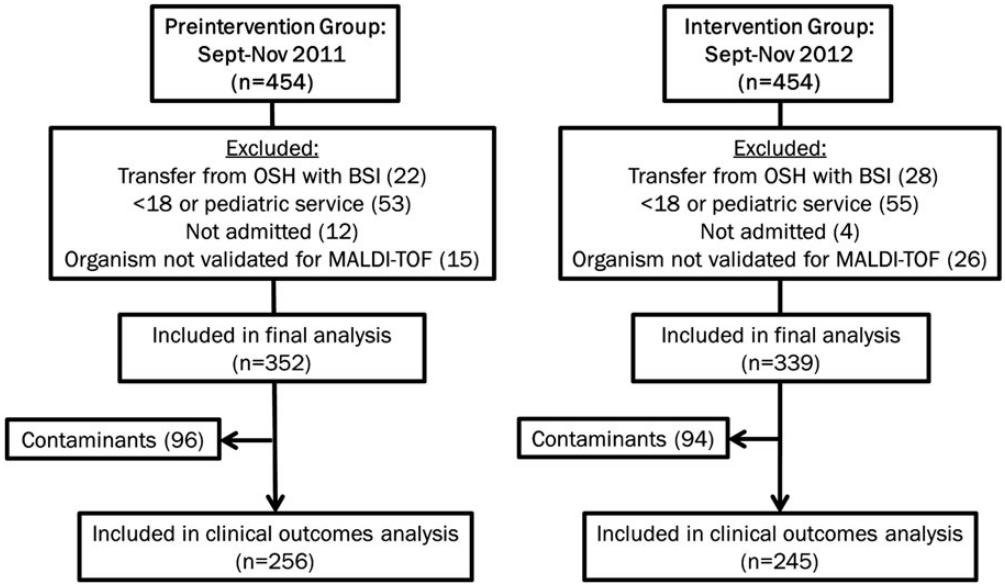

Figure 1. Flowchart of study participants. Abbreviations: BSI, bloodstream infection; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight; OSH, outside hospital.

both groups. Pathogens responsible for BSIs were generally similar between the 2 study periods (Table 2), and there was no difference with regard to prevalence of gram-positive (51.7% vs 55.3%, $P = .571$), gram-negative (41.2% vs 38.0%, $P = .246$), yeast (7.1% vs 6.7%, $P = .753$), and polymicrobial bacteremia (20.3% vs 19.2%, $P = .823$). However, there were more patients in the intervention group with methicillin-resistant *S. aureus* (MRSA) bacteremia (3.7% vs 9.7%, $P = .005$).

Utilization of MALDI-TOF resulted in a significantly shorter time to organism identification (Figure 2), compared to conventional identification methods (84.0 vs 55.9 hours, $P < .001$), and integrating real-time AST review and intervention resulted in improved time to effective therapy (30.1 vs 20.4 hours, $P = .021$) and optimal therapy (90.3 vs 47.3 hours, $P < .001$).

Rapid organism identification combined with MALDI-TOF plus AST intervention was associated with a significant reduction in 30-day all-cause mortality (20.3% vs 12.7%, $P = .021$; Table 3) and improved overall survival by Kaplan-Meier log-rank test ($P = .02$; Figure 3). A nonsignificant reduction in length of hospitalization (14.2 vs 11.4 days, $P = .066$) and significant reduction in ICU length of stay (14.9 vs 8.3 days, $P = .014$) was noted for the intervention group. Additionally, recurrence of BSI with the same organism occurred less frequently in the intervention group (5.9% vs 2.0%, $P = .038$), but there was no difference in 30-day hospital readmission with the same recurrent BSI (3.5% vs 1.6%, $P = .262$). Outcomes were stratified by organism subtype; gram-positive, gram-negative, and yeast (Supplementary Table 1). A significant improvement in mortality was noted during the intervention period for gram-negative bacteremia (25.3% vs 8.3%, $P = .003$), and numerical, nonsignificant improvements were demonstrated across most outcomes, regardless of organism subtype.

The AST made 210 recommendations to prescribers, and 189 interventions (90%) were accepted (Table 4). The AST recommended treatment modifications throughout the microbiology reporting process, with 38.6% of interventions occurring after the availability of organism susceptibility results, 35.7% at organism identification by MALDI-TOF, and 25.7% at time of Gram stain. Nine patients required broadening of therapy following availability of susceptibility results. On further review, the AST had not recommended any changes in therapy that resulted in ineffective treatment for these patients. All 9 patients had notable drug-resistant organisms: 4 patients with *Klebsiella pneumoniae* carbapenemase (KPC)–producing organisms or extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae, 2 patients with persistent MRSA with vancomycin minimum inhibitory concentration of 2 μg/mL, 1 patient with multidrug-resistant *Pseudomonas aeruginosa*, 1 patient with multidrug-resistant vancomycin-resistant enterococci, and 1 patient with fluconazole-resistant *Candida albicans*.

The bivariate analysis and multivariate logistic regression for the aggregate data set identified several factors associated with greater mortality: malignancy, bone marrow transplantation,

Table 1. Patient Baseline Demographics

Baseline Demographics	Preintervention (n = 256)	Intervention (n = 245)	*P* Value
Age, y, mean ± SD	59.5 ± 15.2	56.5 ± 16.3	.030
Female	104 (40.6)	90 (36.7)	.409
Comorbidities, No. (%)			
Malignancy	111 (43.4)	109 (44.5)	.857
Chronic heart disease	110 (43.0)	89 (36.3)	.144
Chronic kidney disease	59 (23.0)	61 (24.9)	.677
Chronic lung disease	43 (16.8)	33 (13.5)	.250
Chronic liver disease	25 (9.8)	31 (12.7)	.321
Solid organ transplant	21 (8.2)	27 (11.0)	.293
Bone marrow transplant	16 (6.3)	25 (10.2)	.142
HIV	0 (0.0)	1 (0.4)	.490
Immunosuppression, No. (%)			
Chemotherapy within 90 d	37 (14.5)	53 (21.6)	.047
Antirejection medications	35 (13.7)	44 (18.0)	.220
Chronic corticosteroids	29 (11.3)	39 (15.9)	.152
ANC <500 cells/μL	8 (3.1)	14 (5.7)	.192
CD4 T cells <200 cells/μL	0 (0.0)	0 (0.0)	>.99
Clinical status, No. (%)			
ICU admission	97 (37.9)	80 (32.7)	.226
Hemodynamic instability requiring vasopressor support	29 (11.3)	31 (12.7)	.681
APACHE III score, mean ± SD[a]	88.7 ± 37.5	87.2 ± 31.6	.842
Source of bacteremia, No. (%)			
Central venous catheter	55 (21.5)	63 (23.7)	.293
Intra-abdominal	53 (20.7)	49 (20.0)	.912
Genitourinary	42 (16.4)	37 (15.1)	.714
SSTI/BJI	26 (10.2)	28 (11.4)	.668
Respiratory	17 (6.6)	12 (4.9)	.448
Foreign device	6 (2.3)	7 (2.9)	.784
Other	9 (3.5)	17 (6.9)	.107
Unknown	48 (18.8)	32 (13.1)	.089
Complications, No. (%)			
Endocarditis	9 (3.5)	18 (7.3)	.074
Metastatic seeding	8 (3.13)	6 (2.4)	.788
Type of acquisition, No. (%)			
Hospital acquired	92 (35.9)	93 (38.0)	.645
Healthcare associated	97 (37.9)	76 (31.0)	.111
Community acquired	67 (26.2)	76 (31.0)	.237

Abbreviations: ANC, absolute neutrophil count; BJI, bone and joint infection; HIV, human immunodeficiency virus; ICU, intensive care unit; SD, standard deviation; SSTI, skin and soft tissue infection.

[a] APACHE III score only reported for patients admitted to the ICU.

Table 2. Organism Distribution

Organism	Preintervention (n = 256), No. (%)	Intervention (n = 245), No. (%)	*P* Value
Total No. of organisms	323	300	
Gram-positive organisms	167 (51.7)	166 (55.3)	.571
Staphylococcus aureus	35 (10.8)	41 (13.7)	.384
MSSA	23 (7.1)	12 (4.0)	.081
MRSA	12 (3.7)	29 (9.7)	.005
Coagulase-negative *Staphylococcus*	51 (15.8)	35 (11.7)	.099
Streptococcus spp	29 (9.0)	40 (13.3)	.120
Enterococcus spp	35 (10.8)	27 (9.0)	.416
E. faecalis	20 (6.2)	14 (4.7)	.379
E. faecium	15 (4.6)	13 (4.3)	.847
VRE	11 (4.3)	10 (4.1)	>.99
Other gram-positive organisms	17 (5.3)	23 (7.7)	.323
Gram-negative organisms	133 (41.2)	114 (38.0)	.246
Escherichia coli	48 (14.9)	43 (14.3)	.817
Klebsiella spp	29 (9.0)	26 (8.7)	.887
Enterobacter spp	18 (5.6)	10 (3.3)	.176
Pseudomonas aeruginosa	12 (3.7)	13 (4.3)	.839
Acinetobacter spp	7 (2.2)	4 (1.3)	.545
Citrobacter spp	5 (1.5)	6 (2.0)	.767
Serratia spp	2 (0.6)	5 (1.7)	.276
Achromobacter spp	1 (0.3)	0 (0.0)	>.99
Other gram-negative organisms	11 (3.4)	7 (2.3)	.475
Yeast	23 (7.1)	20 (6.7)	.753
Candida spp	22 (6.8)	20 (6.7)	.874
Cryptococcus spp	1 (0.3)	0 (0.0)	>.99
Patients with polymicrobial cultures	52 (20.3)	47 (19.2)	.823

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.

ICU status, and older age (Table 5). A nonsignificant trend between improved survival and patients with an accepted AST intervention was observed (odds ratio, 0.55; 95% confidence interval, .28–1.06; $P = .075$).

DISCUSSION

The emergence of rapid diagnostic testing technologies including MALDI-TOF, peptide nucleic acid–fluorescence in situ hybridization (PNA-FISH), and nucleic acid microarrays provides clinical microbiology laboratories with tools to dramatically reduce time to organism identification. The majority of published data evaluating the clinical impact of rapid diagnostic technology involves PNA-FISH, which consistently demonstrates significant improvements in patient outcomes [18]. Furthermore, several PNA-FISH studies have demonstrated

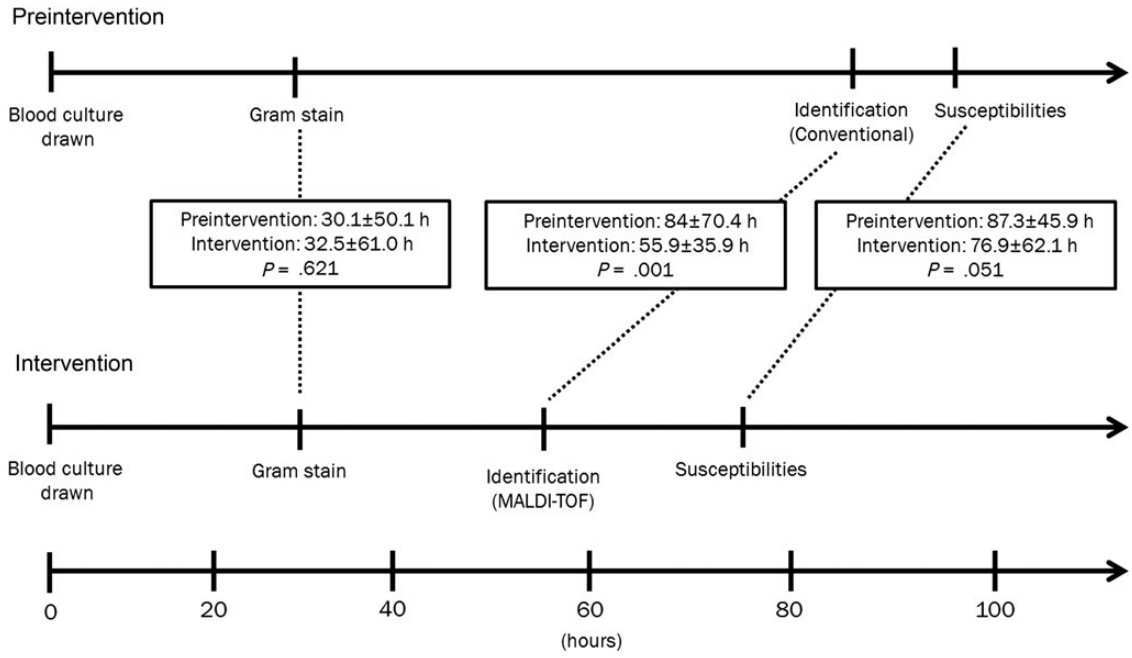

Figure 2. Timeline of microbiological procedures: mean ± standard deviation of time from blood culture draw to Gram stain, organism identification, and susceptibility reporting for both study periods. Abbreviation: MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight.

improved patient outcomes with real-time stewardship intervention in conjunction with rapid diagnostic testing, even when compared to reporting results alone [2, 3, 13, 14, 15]. Although PNA-FISH can provide rapid identification and susceptibility information, this technology is limited by its ability to identify relatively few organisms in a labor-intensive process. In comparison, MALDI-TOF can identify a vastly larger number of organisms via a comparatively simple process.

Table 3. Clinical and Treatment-Related Outcomes

Outcome	Total		
	Preintervention (n = 256)	Intervention (n = 245)	*P* Value
Clinical outcomes			
30-day all-cause mortality	52 (20.3)	31 (12.7)	.021
Time to microbiological clearance, d	3.3 ± 4.8	3.3 ± 5.7	.928
Length of hospitalization, d[a]	14.2 ± 20.6	11.4 ± 12.9	.066
Length of ICU stay, d[a]	14.9 ± 24.2	8.3 ± 9.0	.014
Recurrence of same BSI	15 (5.9)	5 (2.0)	.038
30-day readmission with same BSI	9 (3.5)	4 (1.6)	.262
Treatment-related outcomes			
Time to effective therapy, h	30.1 ± 67.7	20.4 ± 20.7	.021
Time to optimal therapy, h	90.3 ± 75.4	47.3 ± 121.5	<.001

Data are No. (%) or mean ± standard deviation.

Abbreviations: BSI, bloodstream infection; ICU, intensive care unit.

[a] Length of hospitalization and ICU stay were defined as time from blood culture positivity to discharge.

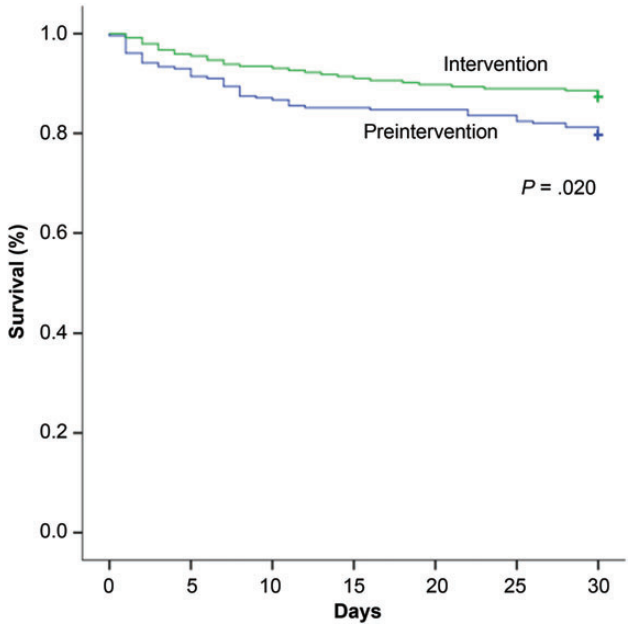

Figure 3. Kaplan-Meier survival analysis: overall survival in both study groups, censored for patients discharged prior to 30 days.

Table 4. Antimicrobial Stewardship Team Interventions

Intervention	Timing of Intervention Recommendation			Total (%)
	Gram Stain	Organism Identification	Antimicrobial Susceptibility	
Narrowed coverage to target the isolated organism	2	22	48	72 (34.3)
Discontinued therapy targeting organisms not isolated	5	44	19	68 (32.4)
Initiated or broadened coverage	39	5	9	53 (25.2)
Other	8	4	5	17 (8.1)
Total (%)	54 (25.7)	75 (35.7)	81 (38.6)	210 (100)
Interventions accepted (%)	49 (90.7)	62 (82.7)	78 (96.3)	189 (90.0)

To our knowledge, this study is the largest and most inclusive study evaluating the clinical impact of MALDI-TOF. Previously published studies include 1 noncomparator observational study, 1 observational cohort study, and 1 quasi-experimental study with stewardship intervention [6, 12, 19]. Clerc and colleagues conducted a prospective observational study and reported that MALDI-TOF identification (without stewardship intervention) was associated with antimicrobial therapy change in 35.1% of patients with gram-negative bacteremia [19]. However, the study observed changes in antibiotic therapy after implementation of MALDI-TOF, and it is unknown if the change in therapy following organism identification was significantly different compared with a control group. Patient outcomes were not reported.

Vlek and colleagues conducted a crossover study of 218 patients with bacteremia in which MALDI-TOF was used for organism identification for 2 months (February 2010 and April 2010) and compared to 2 months of traditional identification (December 2009 and March 2010) [12]. The median time to organism identification occurred 28.8 hours earlier with MALDI-TOF (16.4 vs 45.2 hours, $P < .001$), and significantly improved appropriate therapy within 24 hours of blood culture positivity (75.3% vs 64%, $P = .01$). However, the authors did not evaluate the impact on mortality, length of hospitalization, and other clinical outcomes.

Finally, Perez and colleagues [6] conducted a pre–post quasi-experimental study integrating MALDI-TOF organism identification plus AST intervention, but limited the inclusion to patients with gram-negative bacteremia. They demonstrated a nonsignificant reduction in mortality (10.7% vs 5.6%, $P = .19$), and statistically significant reductions in length of hospitalization (11.9 vs 9.3 days, $P = .01$) and total hospital costs ($45 709 vs $26 126, $P = .009$) [6].

Table 5. Bivariate and Multivariate Unconditional Logistic Regression Analysis for Predictors of Mortality

Variable	Bivariate Analysis[a]			Multivariate Logistic Regression		
	Death (n = 83)	No Death (n = 418)	*P* Value	OR	95% CI	*P* Value
Source of infection						
Genitourinary source	5/78 (6.4)	73/78 (93.6)	.007	0.47	.17–1.32	.152
Respiratory source	9/28 (32.1)	19/28 (67.9)	.034	1.56	.61–4.01	.356
Comorbidities						
Malignancy	47/220 (21.4)	173/220 (78.6)	.011	1.87	1.05–3.33	.032
Bone marrow transplant	11/42 (26.2)	31/42 (73.8)	.085	2.50	1.03–6.03	.042
Solid organ transplant	3/48 (6.2)	45/48 (93.8)	.042	0.38	.11–1.37	.139
Type of organism						
Yeast	9/35 (25.7)	26/35 (74.3)	.155	1.51	.59–3.87	.338
Gram-negative organism	28/183 (15.3)	155/183 (84.7)	.024	0.88	.49–1.61	.687
Other factors						
ICU status	57/177 (32.2)	120/177 (67.8)	<.001	6.45	3.63–11.44	<.001
Age, mean ± SD	57.2 ± 15.8	62.5 ± 15.2	.005	1.02	1.00–1.04	.015
Accepted AST intervention[b]	15/139 (10.8)	124/139 (89.2)	.032	0.55	.28–1.06	.075

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: AST, antimicrobial stewardship team; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; SD, standard deviation.

[a] All sources of infection, comorbidities, types of organisms, and patients on immunosuppressants were included in bivariate analysis and all covariates with $P < .20$ are listed in the table.

[b] Real-time AST interventions only performed during intervention period.

This current study contributes several key advantages compared to previously published literature. First, we analyzed patient outcomes and compared results to a control group, which were lacking in the Vlek et al and Clerec et al publications. Second, Perez and colleagues implemented a similar study design, but lacked the sample size to detect significant differences in mortality. The present study included all positive blood cultures, and did not limit inclusion to a specific subset of organisms (ie, gram-negative pathogens), which is likely a better representation of the daily AST workflow process.

In our study, rapid organism identification by MALDI-TOF combined with AST intervention decreased time to organism identification and time to effective and optimal therapy, which was associated with a decrease in mortality, shorter ICU length of stay, and decreased recurrent bacteremia. However, the study is not without limitations. First, the lack of randomization in our quasi-experimental study may not take into account changes in standard of care over the previous year that could improve mortality. To our knowledge, there were no significant changes in standard of care for patients with BSI during the study periods. Additionally, there may be shifts in hospital ecology or resistance patterns over time. The study periods were selected to minimize chronologic bias of seasonal variation of pathogens and minimize potential maturation bias of medical interns, residents, and fellows at our large academic teaching institution by studying time periods at the same points during training. Furthermore, there are limitations in the time to effective therapy and time to optimal therapy, as antimicrobial administration times were only recorded for inpatients. Antimicrobial administration time in patients who received treatment prior to admission (ie, extended care facilities, clinics, outside hospitals, or emergency departments) was not recorded. Thus, a larger percentage of patients may have been prescribed effective or optimal therapy prior to admission. Additionally, the number and timing of repeat blood cultures to document microbiologic clearance was not standardized and left to prescriber discretion, which may have allowed for variation between different groups. Finally, this study utilized an integrated approach of MALDI-TOF pathogen identification plus real-time stewardship intervention, which makes it difficult to determine the impact of each individual intervention. We evaluated the effect of any accepted stewardship intervention on mortality and demonstrated a nonsignificant trend toward improved survival in multivariate regression analysis. The interventions that improved time to effective therapy were likely those categorized as "started or broadened therapy," which overwhelmingly occurred following notification of Gram stain results, where MALDI-TOF technology did not decrease time to positivity. Although, we feel an integrated approach is optimal, these data suggest that improvements in time to effective therapy are possible with real-time stewardship intervention, even without rapid diagnostic testing.

The responsibility of antimicrobial stewardship programs varies among hospitals, but the overall goal should be to improve patient outcomes and minimize complications [20]. The results of this project, in addition to other publications on rapid diagnostic testing with intervention, suggest that stewardship teams have a significant impact on improving patient outcomes, reducing inappropriate antimicrobial utilization, and reducing costs with real-time review and intervention following culture results. We encourage the expansion of antimicrobial stewardship initiatives that improve patient outcomes, facilitate compliance with quality assurance measures, promote comprehensive disease state management, and ensure appropriate antimicrobial utilization.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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