JPPT | Quality Improvement

Impact of Direct From Blood Culture Identification of Pathogens Paired With Antimicrobial Stewardship Interventions in a Pediatric Hospital

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OBJECTIVE Identification of organisms directly from positive blood culture by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) has the potential for improved clinical outcomes through earlier organism identification and shorter time to appropriate clinical intervention. The uses of this technology in pediatric patients and its impact in this patient population have not been well described.

METHODS Direct from positive blood culture organism identification via MALDI-TOF was implemented in September 2019. A quality improvement project was performed to assess its impact on admissions for contaminant blood cultures and time to effective and optimal antimicrobials and clinical decision-making. A pre- and post-implementation retrospective review for consecutive September through February time periods, was conducted on patients with positive monomicrobial blood cultures. Statistics were evaluated using Mann-Whitney *U* and χ^2 tests.

RESULTS One hundred nineteen patients with 131 unique blood cultures (65 in pre- and 66 in post-implementation) were identified. Time to identification was shorter, median 35.4 hours (IQR, 22.7–54.3) versus 42.3 hours (IQR, 36.5–49) in post- and pre-groups, respectively (p = 0.02). Patients were less likely to be admitted for a contaminated blood culture in the post-implementation, 26% versus 11% in the pre-implementation (p = 0.03) group. In patients treated for bacteremia, there was a shorter time to optimal therapy from Gram stain reporting in the post-implementation (median 42.7 hours [IQR, 27.2–72]) versus pre-implementation (median 60.8 hours [IQR, 42.9–80.6]) (p = 0.03).

CONCLUSIONS Direct from positive blood culture identification by MALDI-TOF decreased time to effective and optimal antimicrobials and decreased unnecessary admission in pediatric patients for contaminated blood cultures.

ABBREVIATIONS ASP, antimicrobial stewardship program; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry

KEYWORDS antimicrobial stewardship; bacteremia; children; matrix-assisted laser desorption-ionization mass spectrometry

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Background

Bloodstream infections are one of the leading causes of morbidity and mortality in hospitalized children and neonates.[1] Early identification of the infecting pathogen is paramount to optimal treatment. Pediatric Surviving Sepsis Guidelines suggest that appropriate antibiotics should be administered within 1 to 3 hours depending on the severity of sepsis.[2] Conventionally, organisms were required to be grown on plate media for 12 to 24 hours prior to identification. However, new commercial platforms boast the ability to identify organisms directly from blood culture, vastly reducing the time to pathogen identification.

Within the last decade, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) has arisen as a reliable method for identification of pathogens from solid plate media and most recently positive blood culture broth.[3] Several laboratories have developed protocols for MALDI-TOF MS identification of organisms directly from blood culture, including those from pediatric patients.[4-10]

In adults, this rapid identification of microorganisms has been shown to reduce time to effective and optimal therapy, as well as mortality, length of stay, and hospital cost.[11-13] Few studies have assessed the clinical impact of direct from positive blood culture identification in pediatric populations. Although a few studies have begun to

investigate this in pediatric patients, these studies have been limited to 1 or 2 daily batches and did not evaluate the impact on readmission for identified blood culture contaminants.[14-16] The aims of this quality improvement project were to confirm if the implementation of organism identification direct from positive blood culture by MALDI-TOF MS impacted time to effective antimicrobial therapy and if implementation would decrease unnecessary antimicrobial use and admissions for blood culture contaminants.

Methods

This quality improvement project was conducted at Connecticut Children's Hospital, a 183-bed pediatric academic medical center in Hartford, CT in conjunction with the Hartford HealthCare Ancillary Microbiology laboratory at Newington, CT where all microbiological testing was performed. The project was deemed exempt from full institutional review board review.

The study population included all patients (age 0–26 years) treated at the children's hospital who had a blood culture obtained that resulted as a mono-microbial organism. Patients were excluded who had blood cultures that were not collected in the emergency department or on the inpatient units. If patients had more than 1 positive blood culture bottle with the same organism for the encounter, only the first was included in the analysis. Multiple positive blood cultures from the same patient with unique organisms, or the same organism but from different admittances were considered as a separate event.

Prior to the implementation of MALDI-TOF MS, blood cultures were collected into BD BACTEC Ped-Plus/F, Aerobic/F, and/or Lytic 10 Anaerobic/F bottles. Once collected by provider, blood cultures were transported to the microbiology laboratory and loaded into the automated incubation BD BACTEC FX system (Becton Dickinson, Sparks, MD). Blood cultures were continuously monitored for 5 days before final reporting of no organism growth. If blood cultures turned positive, the BD BACTEC FX system would automatically alarm, both audibly and with a visual indicator, and these cultures would then be Gram stained and subcultured onto solid agar media plates daily on all shifts. Gram stain results were called to the patient's provider. After at least 12 hours of growth, subcultured plates were read and pure isolates identified by the Bruker MALDI-TOF MS (Bruker Daltonics, Billerica, MA). Organism identification was performed during the hours of 8 am to 4 pm and 11 pm to 7:30 am. If the MALDI-TOF MS score was within the acceptable range, then the genus and species were reported. Most microbes were identified to the species level. Blood cultures positive for common skin flora (e.g., *Bacillus* species, *Corynebacterium* species, viridans group streptococci, and *Cutibacterium acnes*) were not reported to the species level. Susceptibility testing was performed through Becton Dickinson Phoenix, E-test strips (bioMérieux, Marcy l'Etoile, France) and Kirby Bauer, using Clinical Laboratory Standards Institutes breakpoints.[17] Results of organism identification and susceptibilities were uploaded and transmitted to the hospital's electronic medical record system (EPIC Hyperspace 2018) in real time. Organism results were also communicated to care teams via telephone for patients evaluated in both the emergency department and inpatient units. All patients with a positive Gram stain would be admitted (if not already inpatient) and received approximately 2 days of empiric therapy with escalation only occurring in patients who were worsening.

Those in the antimicrobial stewardship program (ASP) participated in daily culture review and feedback 7 days a week. All broad-spectrum antimicrobial prescriptions orders required pre-prescription authorization, which was managed primarily by the infectious diseases pharmacist resident between 8:30 am and 4:30 pm daily. On weekends prior to August 2019 and after hours, the central pharmacist at the hospital provided restricted antimicrobial approval for an initial 48 hours, awaiting approval of the stewardship team. Although the ASP was highly involved in patient care and reviews, at no time during the study was anyone in the program notified by the microbiology laboratory for any positive culture.

The microbiology laboratory validated the use of identification by MALDI-TOF MS using the Bruker Sepsityper IVD kit (Bruker Daltonics) for common monomicrobial organisms directly from positive blood culture over the summer of 2019. Organisms were validated after 30 successful identifications direct from positive blood culture by Sepsityper (Supplemental Table S1). Once blood cultures were flagged positive by the Becton Dickinson BACTEC FX system, specimens were Gram stained to assess for qualification for Sepsityper identification. Specimens to be identified by Sepsityper were batched and performed 4 times daily (4 am, 10 am, 2 pm, and 11:30 pm). Isolate identification was provided to the species level, except in cases of *Streptococcus pneumoniae* and *Escherichia coli*, which were released as presumptive and required further confirmatory testing. Sepsityper organism identification results were uploaded and transmitted to the hospitals electronic medical record system. Laboratory acquisition and implementation cost associated with MALDI-TOF MS instrumentation and Sepsityper has previously been discussed.[3,18-20]

Educational sessions concerning the implementation timeline, in August 2019, and specimen run-times, in October 2019, were provided as continuous quality improvement activities. This education was provided through committee meetings, newsletter publications, and email updates. The Antimicrobial Stewardship Committee also approved of a focused recommendation for optimization of antimicrobial therapy based

Table 1. Baseline Demographics

	Pre-implementation* (n = 65)	Post-implementation† (n = 66)	p value
Age, median (IQR), yr	4.5 (0–10)	3 (0–11)	0.62
Sex, n, %			
Male	38 (59)	34 (51)	0.54
Female	27 (41)	32 (49)	

* September 2018 to February 2019.
† September 2019 to February 2020.

upon organism identified in November 2019. Throughout the time period, the stewardship group continued to perform daily culture and antimicrobial review with feedback to clinicians.

Evaluation and management of patients who had an identified monomicrobial culture performed at the hospital was reviewed for two 6-month periods in consecutive years. The pre-implementation period was from September 1, 2018, to February 28, 2019. The post-implementation period was through September 1, 2019, to February 29, 2020. These time periods were used to account for seasonal variation, as well as to provide a similar expertise of pediatric medical residents prescribing the antimicrobials and the infectious diseases pharmacist residents who assist in the day-to-day stewardship activities.

Patients were identified retrospectively via a blood culture report from TheraDoc (Premier, Inc) and review of the electronic medical record. Data collected included the following: age, sex, organism identified in blood culture, time of pathogen processing (e.g., Gram stain, identification, susceptibility), if patient was admitted to the hospital, and antimicrobial use during admission.

The following definitions were used to assess timeliness of antimicrobial therapy. Time to effective, or organism-directed, therapy was the time from Gram stain to time of administration of first antimicrobial with acceptable organism coverage. Time to optimal therapy was defined as time from Gram stain to narrowest effective therapy based on susceptibility and cessation of unnecessary antimicrobial coverage.

Infections from positive blood cultures included bacteremias, candidemias, central line associated infections, and endovascular infections. Blood culture contaminants were defined as species of coagulase-negative *Staphylococcus*, viridans group *Streptococcus*, *Bacillus* species, *Corynebacterium*, *Micrococcus*, *Lactococcus*, and *Cutibacterium* isolated in only a single specimen, which when evaluated in concordance with patient's medical record review suggested the patient was not immunocompromised or severely ill.

The primary outcomes evaluated included time to effective and optimal therapies and percent of patients admitted for a blood culture contaminant. Before MALDI-TOF MS direct from blood culture identification, the standard of care would be that all patients with a positive Gram stain would be admitted (if not already inpatient) and receive approximately 2 days of empiric therapy with escalation only occurring in patients who were worsening. The goals were to improve the time to effective and optimal therapy for patients with positive blood cultures and reduce admissions for patients with contaminant blood cultures. Secondary outcomes that were evaluated included percent of organisms able to be identified by MALDI-TOF MS direct from positive blood culture, time from Gram stain identification to organism identification, and duration of antibiotic therapies.

Demographics and clinical outcomes were summarized using median and interquartile range (IQR). The differences in the pre- and post-implementation group were assessed with a Mann-Whitney *U* test. Organism distribution was analyzed using χ^2 tests. Statistical significance was set at 2-tailed $p < 0.05$.

Results

There were 137 positive blood cultures. Six (2 in the pre-implementation and 4 in the post-implementation) were polymicrobial and were excluded, leaving 131 monomicrobial blood culture bottles identified from 119 patients, 65 in the pre-implementation group and 66 in the post-implementation group. The median age of all patients was 4 years (IQR, 0–11 years) and 55% were male. There was no statistical difference in age or sex between the pre- and post-implementation groups (Table 1).

The implementation of MALDI-TOF MS direct from blood culture 4 times daily had a significant impact on readmission of patient for treatment of bacteremia, with 11% in the pre-implementation versus 26% in the post-implementation groups never being treated for bacteremia, $p = 0.03$). Organisms identified for these patients included the following: 6 patients (86%) in the pre-implementation group with non-pathogenic *Staphylococcus* species and 1 group A Streptococcus. Organisms treated as contaminants in the post-implementation group included the following: 9 (53%) non-pathogenic *Staphylococcus*, 4 (24%) *Streptococcus* species, 2 *Kocuria rhizophila*, 1 *Rothia mucilaginous*, and 1 *Bacillus cereus*.

In patients with pathogens identified, those in the post-implementation group had a significantly

Table 2. Length of Antibiotic Therapy Outcomes in Patients Treated for Infections With Positive Blood Cultures

	Pre-implementation* (n = 56)	Post-implementation† (n = 48)	p value
Time from Gram stain to organism-directed therapy, median (IQR), hr	42.3 (15.3–57.7)	21.5 (13–37.5)	0.02
Time from Gram stain to optimal therapy, median (IQR), hr	60.8 (42.9–80.6)	42.7 (27.2–72)	0.03
Time from empiric antibiotic start to optimal therapy, median (IQR), hr	72.9 (55.9–110.1)	53.2 (24.4–83.8)	0.007

* September 2018 to February 2019.
† September 2019 to February 2020.

Table 3. Successful Identification of Pathogen Direct From Positive Blood Culture (Post-implementation)

Month	All Organisms Identified		Organisms Successfully Identified Direct from Positive Blood Culture
	Total, n	Validated, n	Total, n (% validated)
September	17	15	8 (47)
October	7	6	5 (83)
November	12	10	6 (60)
December	16	11	11 (100)
January	8	7	5 (71)
February	6	5	4 (80)

decreased time to change in empiric antibiotics to organism-directed therapy from Gram stain (p = 0.02) (Table 2). In the pre- and post-implementation group, respectively, 29% versus 27% of patients required escalation of therapy, 59% versus 56% had therapy de-escalated to narrower antimicrobial therapy, and 10% versus 19% had therapy discontinued. Time to optimal antibiotics was also significantly shorter in the post-implementation group, with a median reduction in time from Gram stain and empiric antibiotic start to optimal therapy (p = 0.03 and p = 0.007, respectively) (Table 2).

In the post-implementation group, 59% of organisms were able to be identified directly from positive blood culture bottles by MALDI-TOF MS. During the 6-month post-implementation period, there was not an increase in percentage of successful attempts in direct from positive blood culture identification (Table 3). A large percentage of *E coli* and *Staphylococcus aureus* were not successfully identified directly from positive blood culture bottle, with 67% of *E coli* and 40% of *S aureus* not successfully identified by Sepsityper. Common organisms that were validated early (e.g., *Staphylococcus not-aureus*, *Streptococcus* species, and *E coli*) showed significant decrease in time to organism identification (Supplemental Table S1). The most common organisms identified were coagulase negative *Staphylococcus* species (i.e., *Staphylococcus epidermidis*, *Staphylococcus hominis*, *Staphylococcus warneri*, *Staphylococcus capitis*, and *Staphylococcus lugdunensis*) and *S aureus* (Table 4). The distribution of organisms was similar between groups, except for a higher rate of *Enterobacter cloacae complex* identified in the pre-implementation group (Table 4).

MALDI-TOF MS direct from positive blood culture bottle identification was also found to decrease the median time to organism identification from 42.3 (IQR, 36.6–49) to 35.4 (IQR, 22.7–54.3) hours, p = 0.02, in the pre- and post-implementation group, respectively. A subanalysis of time from Gram stain to organism identification per organism can be found in the Supplemental Table S2. No significant difference was detected in time from Gram stain to susceptibility results, at 47.6 hours (IQR, 43.1–63.4) in the pre-implementation and 47.5 hours (IQR, 38.7–63.9) in the post-implementation groups (p = 0.69).

Discussion

This is one of the first pediatric studies to evaluate the impact of MALDI-TOF MS direct from positive blood culture on patient care. It is the first to our knowledge to show a decrease admission rate from blood culture contaminants. Admissions for contaminated blood cultures, typically due to skin flora caused by errors during the specimen collection process, account for substantial costs to the health care system, leading to unnecessary

Table 4. Organism Distribution

	Pre-implementation (n = 65)	Post-implementation (n = 66)
Gram-positive organisms, n (%)	40 (61.5)	49 (74.2)
Staphylococcus aureus	8 (12.3)	10 (15.2)
Pathogenic *Staphylococcus non-aureus* species*	1 (1.5)	0
Non-pathogenic staphylococci†	15 (23.1)	18 (27.2)
Group A Streptococci	1 (1.5)	0
Group B Streptococci	3 (4.6)	3 (4.5)
Streptococcus hemolyticus	1 (1.5)	0
Streptococcus pneumoniae	0	3 (4.5)
Viridans Streptococci‡	4 (6.2)	5 (7.6)
Enterococcus species§	4 (6.2)	2 (3)
Kocuria (*Micrococcus luteus*) *rhizophila*	1 (1.5)	4 (6.1)
Rothia mucilaginosus	0	2 (3)
Other Gram-positive organisms¶	2 (3.1)	2 (3)
Gram-negative organisms, n (%)	24 (36.9)	15 (22.7)
Acinetobacter species	0	1 (1.5)
Citrobacter freundii complex	1 (1.5)	0
Escherichia coli	7 (10.7)	6 (9.1)
Enterobacter cloacae complex	5 (7.7)	0
Klebsiella species	4 (6.2)	2 (3)
Proteus mirabilis	1 (1.5)	0
Morganella morganii	0	1 (1.5)
Pseudomonas aeruginosa	2 (3.1)	0
Serratia marcescens	1 (1.5)	0
Bacillus species	1 (1.5)	3 (4.5)
Neisseria species	1 (1.5)	1 (1.5)
Other Gram-negative organisms#	1 (1.5)	1 (1.5)
Candida species**	1 (1.5)	2 (3)

Note; quantity of each organism identified included in parentheses

* Pre-implementation group: *Staphylococcus lugdunensis*.

† Coagulase-negative staphylococcus identified included; pre-implementation: *Staphylococcus capitis*, *Staphylococcus epidermidis* (n=9), *Staphylococcus hominis* (n=4), *Staphylococcus lugdunensis*, *Staphylococcus warneri*; post-implementation: *Staphylococcus capitis*, *Staphylococcus epidermidis* (n=11), *Staphylococcus hominis* (n=5), *Staphylococcus warneri*.

‡ Streptococci species identified: pre-implementation: *Streptococcus mitis/oralis* (n=3), *Streptococcus salivarius*; post-implementation: *Streptococcus mitis/oralis* (n=3), viridans group *Streptococcus*, *Streptococcus salivarius*.

§ *Enterococcus* species: pre-implementation: *Enterococcus faecalis* (n=3); *Enterococcus faecium* (n=1); post-implementation: *Enterococcus faecalis* (n=2).

¶ Other Gram-positive organisms: pre-implementation: *Lactobacillus*, *Lactococcus*; post-implementation: *Corynebacterium*, *Cutibacterium acnes*.

Other Gram-negative organisms: pre-implementation: Haemophilus influenza; post-implementation: *Salmonella* species.

** Candida species: pre-implementation: *Candida parapsilosis*; post-implementation: *Candida krusei*, *Candida lusitaniae*.

antimicrobial treatment, diagnostic procedures, and extended hospital stays.[21,22] Although adult studies have shown that use of direct from positive blood culture identification has decreased hospital and ICU length of stays, this has not been able to be reliably shown in pediatric data.[11-15] Our quality improvement study showed that direct from positive blood culture bottle identification by MALDI-TOF MS was associated with reduced admissions for blood culture contaminants. In the pre-implementation group, 11% of patients were not readmitted for a positive blood culture; the decision was based on the medical team's clinical decision-making, often in conjunction with infectious diseases consultation. In the post-implementation group, 26% of patients with blood culture contaminants avoided hospital inpatient admission after being seen in the emergency department. Availability of earlier blood culture identification helps support the medical team's clinical decision-making, as well as avoid unnecessary costs to both the hospital and patient's family. This is also important as a previous report by Messacar et al[23] showed similar results using BioFire FilmArray blood culture identification, another rapid organism identification technology, but this is the first time similar data were shown for using MALDI-TOF MS identification from positive blood culture in children.[23]

In addition to the impact on admissions, we demonstrated that MALDI-TOF MS direct from positive blood culture identification combined with ASP interventions significantly decreased time to organism-directed and optimal therapy in patients treated for bacteremia. This is

in agreement with many adult studies, which have shown that MALDI-TOF MS resulted in significant decreases in time to both effective and optimal therapy.[11-13,24] The number of pediatric studies assessing the impact of this technology are far fewer, but are also in agreement with our results, which showed significantly shortened time to organism identification and optimal therapy.[14-16] In contrast to earlier pediatric studies, this investigation did not find a significantly shorter time to susceptibility results, which in previous studies has been thought to contribute to earlier optimal therapy.[14,15] In this quality improvement study, the time to earlier optimal therapy may be in part due to additional antimicrobial stewardship interventions and implementations, including recommendations to discontinue unnecessary antimicrobial coverage and escalation of therapy for identified organisms with known resistance patterns due to organism-specific recommendations implemented in November 2019. In contrast to previous reports, this report also showed a statistically significant decreased time to effective, or organism-directed, therapy. In the 2 previous pediatric reports both Malcolmson et al[14] and Bhavsar et al,[15] a reduction in time to effective therapy was trending, but did not reach statistical significance.

There are some significant differences that distinguish this quality improvement project from previous pediatric evaluations and may explain why results diverge. First, the number of times MALDI-TOF MS was performed daily differed between this study and those previously published. Bhavsar et al[15] reported samples to be identified by MALDI-TOF MS were consolidated into 2 batches to be performed daily and cultures identified later in the day were plated to solid media. In this evaluation, 4 batches were done, occurring both during day and night shifts. This allows for more real-time results and helps to avoid extended delays in identification in blood cultures that become positive during the nighttime period. Secondly, this is the first report to show the potential added benefit of 7 days per week antimicrobial stewardship support. The provision of prospective audit and feedback 7 days per week helped to ensure both effective and optimal antimicrobial use.

Like any investigation there are potential limitations. First, this investigation included a small time period and number of blood cultures from a single center, making results potentially difficult to extrapolate to other centers. Secondly, this was a retrospective investigation, which may come with potential biases that are inherent to retrospective review of patient charts. Thirdly, between the pre- and post-implementation phases, the ASP expanded from weekdays to 7 days per week for pharmacist staffing and prospective audit and feedback, which may confound time to changes in antibiotic therapy. Finally, the post-implementation phase was conducted during a period where organisms continued to be validated by the microbiology laboratory, which may confound the MALDI-TOF MS data and as such its potential full benefit may have been underestimated. However, by assessing the impact during organism validation and demonstrating an early statistically significant difference, our quality improvement shows that MALDI-TOF MS paired with antimicrobial stewardship can be effective even with only a few, but key organisms validated.

Conclusion

Use of direct from positive blood culture bottle identification by MALDI-TOF MS combined with antimicrobial stewardship support and interventions has resulted in a decrease of admissions for contaminated blood cultures and significant decreases in the time to organism-directed and optimal therapy in a pediatric hospital. Additional studies are warranted to evaluate if similar data are seen at other institutions.

Article Information

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