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ORIGINAL ARTICLE

The implementation of rapid microbial identification via MALDI-ToF reduces mortality in gram-negative but not gram-positive bacteremia

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Abstract

Our goals were to study the effect of rapid microbial identification (RMI) of positive blood culture on patient's outcome and to identify specific microbiological characteristics related to clinical benefit of RMI. This was a retrospective-cohort study of hospitalized, adult patients with bacteremia. The outcome of patients with bacteremia episodes was compared before vs. after the initiation of RMI. RMI was done by matrix-assisted laser desorption/ionization time-of-flight testing of microcolonies. The study included 1460 and 2710 cases in the pre- and post-intervention periods, respectively. There were similar rates of gram-negative, gram-positive, anaerobes, and polymicrobial infections, but higher rate of contaminants in the intervention period (39.9 vs. 43.7%, $p = 0.019$). The median time-to-identification decreased from 47.5 to 21.3 h ($p < 0.001$). Post-intervention, the median LOS declined from 10.83 to 9.79 days ($p = 0.016$), the rate of ICU transfer declined from 13.8 to 11.6% ($p = 0.054$), and the mortality rate declined from 20.9 to 18.3% ($p = 0.047$). The improvement in outcome variables remained statistically significant in multivariate analysis when performed for all episodes and non-contaminants but not for contaminants. The mortality declined in gram-negative bacteremia (20% vs. 15.5%, $p = 0.005$ in multivariate analysis) but not in gram-positive bacteremia (18.1% vs. 18.5%). RMI reduces mortality from gram-negative but not gram-positive bacteremia.

Keywords Rapid identification · Bacteremia · Mortality · MALDI-ToF · Gram-negative

Background

Prompt identification of bloodstream infections (BSI) pathogen in and its susceptibility to antimicrobials are essential for the selection of appropriate treatment [1]. BSI is diagnosed through a multi-phase processing of positive blood culture, where the first stage is a preliminary identification by a gram-stain. However, this preliminary result may not be sufficient, especially in cases of antimicrobial-resistant (AMR) organisms (e.g., *Acinetobacter baumannii*) and thus the final microbial identification may be crucial for appropriate selection of antimicrobials [2]. Two relatively novel methods allow rapid microbial identification (RMI): (1) PCR-based methods and (2) matrix-assisted desorption ionization–time-of-flight (MALDI-ToF) mass spectrometry-based methods. Both are typically applied as "add-on "methods in addition to the regular diagnostic practice and their application pose significant financial and technical challenges [1]. Hence, the justification for their application should include evidence for clinical benefit and not merely analytical-diagnostic arguments. The vast majority of studies have defined treatment-based variables, such as time-to-targeted therapy as their primary outcome measure [1]. Most studies have not looked or were unable to present benefit in terms of patient outcomes, such as mortality or ICU transfer rates [3]. Moreover, most studies that were able to show improvement in patient outcome have combined dedicated antimicrobial stewardship programs (ASP) [4–6]

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and thus the net effect of the methodological changes (vs. the combined effect) cannot be elucidated from these studies. Other studies that compared RMI alone vs. combined RMI with dedicated ASP have found inferior results in the RMI-only group [3, 7].

Since January 2016, we initiated RMI of positive blood cultures at the Tel-Aviv Sourasky Medical Center (TASMC) by analyzing microcolonies using MALDI-ToF [8]. This change in the laboratory practice was not accompanied by a targeted change in the ASP. The goals of this study were (1) to study the effect of RMI of positive blood culture on patient's outcome and (2) to identify specific microbiological characteristics related to clinical benefit of RMI.

Materials and methods

Setup The Tel-Aviv Sourasky Medical Center is a 1,500-bed, tertiary care center and is the only general hospital serving the population of Tel-Aviv, Israel. Antimicrobial stewardship program is implemented via a system of mandatory pre-authorization by an Infectious Diseases consultant of a defined list of restricted antimicrobials, elective individual patient consultations, and institutional guidelines for antimicrobial use. Antibacterial usage at each period is presented at table S1. Microbiological reports are issued via a computerized system with the exception of "panic" values, including the initial gram-stain morphology of positive blood cultures that are reported by phone. Other stages of blood culture results are not reported by phone.

Study design This was a retrospective-cohort study of adult patients with positive blood culture (bacterial only) comparing patient outcomes between two periods, before (January 2014–December 2015) and after (January 2016–April 2018) the implementation of RMI. RMI was implemented only during the morning weekday's hours. Hospital staffs, including Infectious Disease specialists, were informed via written and oral communications about the availability of this service and were reviewing the RMI results on a regular basis.

The inclusion criteria for the study included (1) age ≥ 18 years; (2) bacterial morphology identified on direct gram-stain from a positive blood culture, and (3) direct gram-stain report issued while the patient was still hospitalized. Since RMI (i.e., the intervention) was performed only during the morning hours on weekdays (see above), we included only cases where direct gram-stain report was issued during those hours in both periods (before and after intervention).

The study was approved by the institutional Ethics Committee.

Microbiological methods and definitions Blood cultures were analyzed using the BACT/ALERT® 3D® system (2014-July 2017) or the VIRTUO® system (August 2017-present) (both by bioMerieux, Marcy l'Etoile, France). RMI was done by analyzing microcolonies using the VITEK-MS® MALDI-ToF [8] (bioMerieux, Marcy l'Etoile, France). Otherwise, identification was performed by MALDI-ToF after a ~14–48 h of incubation. Direct antimicrobial susceptibility testing (AST) from positive blood culture was routinely done by disk diffusion throughout the study. Confirmatory, final AST was done by the VITEK2® system (bioMerieux, Marcy l'Etoile, France) and was performed on "mature" colonies (following ~16–18 h incubation) during the first period or on microcolonies (following ~4–6 h incubation) during the second period and interpreted according to CLSI criteria [9]. Contaminants were defined as single isolation of the following bacteria: coagulase-negative Staphylococci, *Micrococcus* spp., *Propionibacterium* spp., "Viridans"-type Streptococci, *Bacillus* spp., and *Corynebacterium* spp. "Polymicrobial" episode was defined as the isolation of ≥ 2 different species (simultaneously or within 3 days), of which at least one was not a contaminant.

Data analysis Data were extracted from the hospital database using Microsoft SQL server. For each case, the time reference points in the process of blood culture analysis were defined as follows: (A) reception of blood culture in the lab; (B) gram-stain report of positive blood culture; (C) final identification of the pathogen(s); (D) final AST report. In cases where the final identification was preceded by a preliminary identification (e.g., "gram-negative bacilli" followed by *Klebsiella pneumoniae*), an attribution logic of final vs. preliminary identification was applied as described in table S2. In polymicrobial episodes (as defined above) or cases with more than one monobacterial episode, the time points considered for data analysis were those obtained for the last pathogen identified.

Outcome measures included (a) the bacteremia eradiation rate, calculated as the rate of blood culture sterilization after 3 days from the initial positive culture; (b) total length of stay (LOS); (c) rate of transfer to ICU; and (d) in-hospital mortality. Outcome analysis was done for the entire cohort and according to the following stratifications: (1) contaminant vs. non-contaminant bacteria; (2) gram-positive vs. gram-negative bacteria. Since the data regarding antimicrobial therapy was not accessible to our data mining system throughout most of the study, this data was not included.

Statistical analysis was performed using R and RStudio statistical software (versions 3.3.3 and 1.1.423, respectively). Univariate tests included *t* test and the Wilcoxon rank-sum test for continuous variables, and chi-squared test for dichotomic and categorical variables. Linear regression models for continuous outcome measures (TTNB, LOS) were fit with log-transform of the dependent variable. Logistic regression models were fit for dichotomic outcome measures (negative culture in 3 days, ICU transfer, in-hospital mortality). The models included the following background and hospitalization variables: age, Charlson comorbidity index (CCI), contamination (if applicable), polymicrobial episode (if applicable), surgery during hospitalization, time from reception of blood sample to gram-stain report, and time from gram-stain report to final identification.

Results

Baseline characteristics of patients and microbiological features of BSI cases in the two periods

A total of 15,531 patients with positive blood cultures were identified during both study periods, of which 12,493 met the inclusion criteria. Direct gram-stain report was issued during the morning in 4,170 cases that entered into the final analysis, 1460 and 2710 in the pre- and post-intervention periods, respectively. The demographic characteristics and microbiological features (bacterial groups and main organisms) of BSI cases are presented in Table 1. Patients in the intervention period were older and had higher severity of underlying morbidities, as evaluated by CCI. Although the distribution of admitting departments was similar, patients in the intervention period had higher rate of surgery performed during their hospitalization.

The distribution of the main bacterial groups was similar in the two groups as well as the main bacterial species, with the exception of lower rate of *Acinetobacter baumannii* infections in the intervention group (4 vs. 1.6%, $p < 0.001$). Overall, there was higher rate of contaminants in the intervention group (39.9 vs. 43.7%, $p = 0.019$) and coagulase-negative Staphylococci (CONS) were by far the most common organism in both groups (44.9 and 45.2%). Polymicrobial infections were slightly less common in the intervention group (10.4 vs. 8.6%, $p = 0.061$).

Overall and differential effects of the intervention on patient outcomes

Following the initiation of the intervention, RMI (TTI ≤ 6 h) was performed in 47% of episodes (Table 1). The median TTI and time-to-AST (TTA) was reduced in 55% and 50%, respectively, while the time from reception to gram-stain had declined in only 5.6% (Table 1, Fig. 1). There was no significant change in the rate of negative culture by day 3, which was already high in the pre-intervention period (83.2 vs. 84.2%). In all other outcome measures, there was a significant improvement in the intervention period, including a 12.4% decline in in-hospital mortality (Table 2). In order to better define the added value of the intervention in different microbiological groups, we evaluated the effect on patient outcomes stratified to microbiological sub-groups, including gram-positive vs. gram-negative and contaminants vs. non-contaminants BSI (Table 2). The beneficial effects of the intervention were absent in both gram-positive and contaminants strata but remained significant in almost all measures (with the exception of "negative culture in 3 days") in gram-negative and non-contaminants; in-hospital mortality declined by 22.5% and 18.9% in gram-negative and non-contaminants, respectively.

Since the population in the intervention period was generally older and sicker, we evaluated the effect of TTI on the outcome measures in a multivariate model that included demographic-clinical variables (age, Charlson score, and surgical procedure during hospitalization), microbiological variables (contaminants and polymicrobial BSI), and the time interval from culture reception to gram-stain report along with the TTI itself. This had allowed us to examine the net effect of TTI, since RMI was de-facto performed in only 47% of the cases (Table 1). The effects of variables other than the TTI are presented in table S3. When the model included all cases, the reduction of TTI was correlated with significant improvement in both the LOSs, rate of ICU transfer, and in-hospital mortality (Table 3). Likewise, these effects remained significant in non-contaminants and gram-negative; in the latter, the effect on ICU transfer became non-significant in the multivariate model. Similar to the univariate analysis, reduction of TTI was not correlated with beneficial effects in gram-positive and in the contaminants groups, with the exception of reduced LOS in gram-positive.

Discussion

A variation of the MALDI-ToF-based RMI is the performance of the test on microcolonies (after 4–6 h of incubation), rather than on an extract from the blood culture. Although this method does require the availability of MALDI-ToF, it allows a relatively simpler operation and a shorter hand-on-time, and does not require additional kits [8]. This method was evaluated in several analytical studies [10–13] that validated its usefulness and accuracy, but its clinical impact was only partially evaluated in a study that analyzed the effect of an intervention that included the use of MALDI-ToF on both microcolonies and on blood-culture extract, combined with rapid antimicrobial-resistance phenotypic assays and ASP [14]. The authors found a significant reduction in time-to-optimal therapy but other clinical outcomes were not measured. Therefore, our study is the first to evaluate the net effect on clinical outcomes of RMI using MALDI-ToF on microcolonies and to the best of our knowledge, the RMI study with the largest cohort reported so far, which provided

Table 1 Demographic characteristics and microbiological features of bacteremia cases throughout the study

Variable, *n* (%)	Period		*p* value
	Pre-intervention (*n* = 1460)	Post-intervention (*n* = 2710)	
Mean age (SD)	69.6 (18.37)	71.4 (17.96)	0.002
Sex, % female	669 (45.8)	1246 (46.0)	0.949
Charlson comorbidity index (%)			< 0.001
Mild (CCI 0–2)	354 (24.2)	525 (19.4)	
Moderate (CCI 3–5)	622 (42.6)	1044 (38.5)	
Severe (CCI 6+)	484 (33.2)	1141 (42.1)	
Admitting department			0.895
Internal medicine	1021 (69.9)	1882 (69.4)	
Surgical services	230 (15.8)	448 (16.5)	
Intensive care units	91 (6.2)	171 (6.3)	
Hematology/oncology	36 (2.5)	72 (2.7)	
Other services	82 (5.6)	137 (5.1)	
Surgery during hospital stay	253 (17.3)	613 (22.6)	< 0.001
Contaminants only	582 (39.9)	1184 (43.7)	0.019
Polymicrobial	152 (10.4)	233 (8.6)	0.061
Gram-positive bacteria	1021 (69.9)	1917 (70.7)	0.611
Coagulase-negative Staphylococci	656 (44.9)	1225 (45.2)	0.892
Staphylococcus aureus	96 (6.6)	175 (6.5)	0.935
Streptococcus viridans group	90 (6.2)	178 (6.6)	0.659
Corynebacterium spp.	55 (3.8)	110 (4.1)	0.705
Enterococcus faecalis	57 (3.9)	114 (4.2)	0.698
Gram-negative bacteria	577 (39.5)	1010 (37.3)	0.163
Escherichia coli	262 (17.9)	497 (18.3)	0.785
Klebsiella pneumoniae	105 (7.2)	169 (6.2)	0.262
Pseudomonas aeruginosa	52 (3.6)	96 (3.5)	1
Acinetobacter baumannii	59 (4.0)	44 (1.6)	< 0.001
Proteus mirabilis	37 (2.5)	63 (2.3)	0.752
Anaerobe	13 (0.9)	36 (1.3)	0.271
Median time (h) from reception to gram-stain report (IQR[1])	24.44 [20.60, 26.98]	23.07 [18.88, 26.43]	< 0.001
Time (h) from gram-stain report to identification Median (IQR[1])	47.48 [26.73, 52.44]	21.29 [4.27, 25.50]	< 0.001
Categorical (%)			< 0.001
< 6 h	4	47	
6–12 h	0.3	1.3	
2–24 h	4.7	16.3	
> 24 h	91	35.4	
Median time (h) from gram-stain report to AST report (IQR[1])	50.04 [47.20, 71.55]	25.02 [23.17, 47.58]	< 0.001

[1] IQR interquartile range

us with enough statistical power to analyze the effect on several outcome measures.

Our study found that the intervention resulted in an overall significant beneficial effect on patient's outcome measures in multivariate analysis, including shorter LOS, lower rate of ICU transfer, and reduced mortality (Table 3). To the best of our knowledge, our study is the first where RMI was proven to reduce mortality in multivariate analysis. The effect of RMI on mortality was not analyzed in many of these studies [1] and the results were inconsistent in those who did. One study where fluorescence in situ hybridization (FISH) testing was used on positive blood cultures with gram-positive cocci in clusters reported reduced mortality following the intervention. These results were not tested in multivariate analysis and were

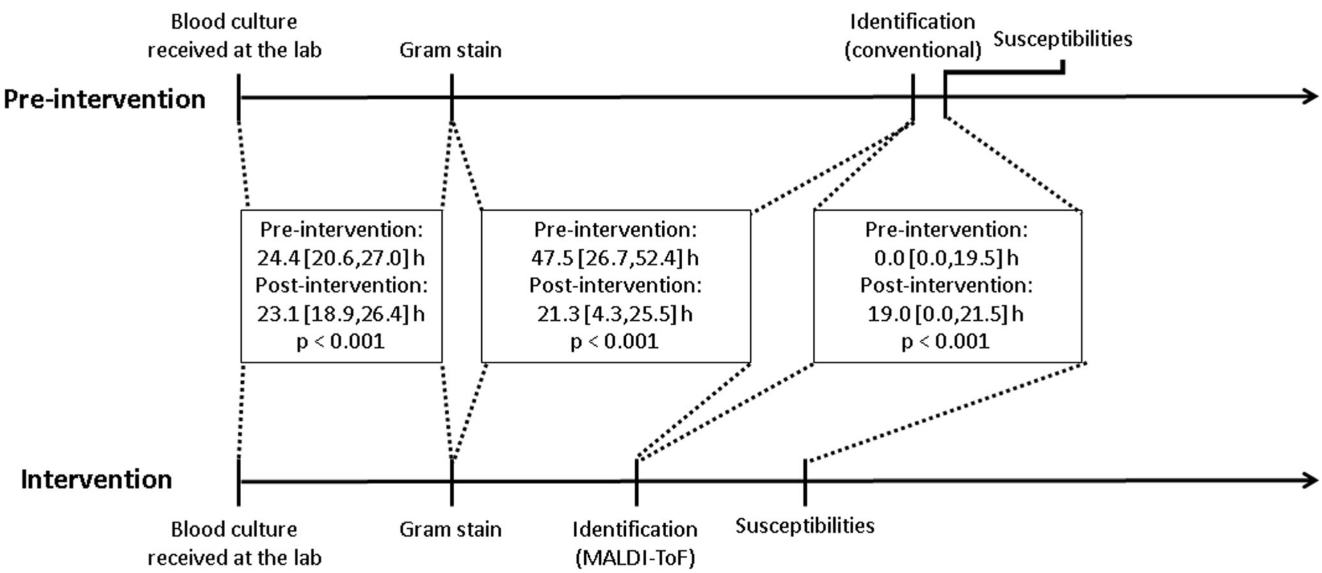

Fig. 1 The effect of rapid identification on positive blood culture timelines

somewhat surprising, since the beneficial effect of the intervention was noted also in coagulase-negative staphylococci (CONS) that are mostly contaminants [4]. No benefit in terms of mortality was found in two large studies that used multiplex PCR [3, 15], despite reduction in the treatment-related time intervals. On the other hand, a large pre/post-intervention study that used MALDI-ToF [16] found reduced mortality in the intervention group that was significant in univariate analysis but not in the multivariate analysis ($p = 0.075$). Since the size of the cohort in that study [16] was smaller compared with our study, it is likely that this effect would have been verified, had the population size been larger.

In this study, we examined whether there are microbiological sub-groups where the effect of TTI reduction can be the most beneficial. We found that with most outcome measures, the beneficial effect was significant in gram-negative bacteria (vs. gram-positive) and in non-contaminants. To the best of our knowledge, our study is the first to perform

Table 2 Crude overall and stratified differences in patient's outcome measures according to period

Variable, *n* (%)	Period		*p* value
	Pre-intervention ($n = 1460$)	Post-intervention ($n = 2710$)	
Median length (days) of stay (25–75% IQR)			
All cases	10.83 [5.34, 23.91]	9.79 [5.08, 21.69]	0.016
Gram-positive bacteria	9.19 [4.86, 21.14]	8.86 [4.62, 20.35]	0.295
Gram-negative bacteria	11.51 [6.15, 23.83]	9.88 [5.86, 18.89]	0.017
Contaminants	7.63 [4.35, 17.18]	7.27 [4.16, 16.85]	0.342
Non-contaminants	13.18 [6.72, 28.54]	11.90 [6.58, 25.94]	0.068
Transfer to ICU (%)			
All cases	189 (13.8)	295 (11.6)	0.054
Gram-positive bacteria	97 (11.9)	171 (10.8)	0.478
Gram-negative bacteria	49 (11.9)	77 (10.5)	0.554
Contaminants	51 (9.1)	98 (8.7)	0.854
Non-contaminants	138 (17.0)	197 (13.9)	0.055
In-hospital death (%)			
All cases	305 (20.9)	496 (18.3)	0.047
Gram-positive bacteria	158 (18.1)	312 (18.5)	0.817
Gram-negative bacteria	86 (20.0)	120 (15.5)	0.054
Contaminants	92 (15.8)	195 (16.5)	0.775
Non-contaminants	213 (24.3)	301 (19.7)	0.01

[1] IQR interquartile range; [2] negative culture existed in 64.1 and 62% of cases in the two periods ($p = 0.181$)

Table 3 Overall and stratified multivariate analysis of the effect of time-to-identification on the outcome measures

Bacterial group (no. of cases in pre-intervention/ intervention)	Length of stay, log-link linear coefficient (*p* value)	Transfer to ICU, adjusted O.R. (*p* value)	In-hospital mortality, adjusted O.R. (*p* value)
All cases (1460/2170)	0.0023 (0.001)	1.007 (0.0019)	1.004 (0.0123)
Gram-positive (874/1683)	0.0016 (0.0315)	1.004 (0.16)	1.0008 (0.72)
Gram-negative (430/776)	0.0025 (0.011)	1.005 (0.26)	1.01 (0.005)
Contaminants (582/1184)	0.0006 (0.45)	1.005 (0.2)	1.00 (0.86)
Non-contaminants (878/1526)	0.003 (> 0.0001)	1.007 (0.004)	1.006 (0.0018)

The results of the other variables that were included in the model (age, Charlson score, surgical procedure during hospitalization, contaminants, polymicrobial BSI, and the time interval from culture reception to gram-stain report) are presented in table S3

microbiologically stratified outcome analysis of RMI intervention, which was possible thanks to the large size of the cohort. Previous studies examined the effect of RMI of specific pathogens on patient's outcome. Most of these studies had a pre/post-intervention design and in all of them, the intervention was combined with ASP. Two studies examined the effect of RMI in MDR-gram-negative bacteremia [17] and in *A. baumannii* infections [18]. In both studies, the intervention led to reduction in the time-to-optimal therapy, but reduced mortality was found only in the MDR-gram-negative study. Studies in gram-positive bacteria were done mostly on *Staphylococcus* spp., either CONS [19, 20] or *S. aureus* [21], and all reported improvement in various antimicrobial treatment-related variables (e.g., duration of unnecessary treatment), but did not report improvement in mortality or other patient-related variables. Overall, the results of these studies are in accordance with our findings and are understandable since unlike gram-negative bacteria, the vast majority of *Staphylococcus* species in blood cultures are contaminants and thus their rapid identification is unlikely to affect the mortality rate of the corresponding patients. On the other hand, most cases of gram-negative bacteremia are true infections and in many cases, require different therapeutic approach, even prior to AST reports (e.g., *E. coli* vs. *P. aeruginosa* vs. *A. baumannii*).

The most problematic part of our study is the lack of data regarding antimicrobial therapy, since the clinical value of RMI is exerted via the potential for rapid change in treatment. This shortcoming is a result of our computerized data mining method, which had allowed us to analyze a large dataset on the one hand but did not include treatment data on the other hand. Although individual patient's data was missing, the overall usage of antibacterial agents remained relatively stable throughout the two study periods (table S1). Thus, it is hard to elucidate concrete policy change in the overall antibacterial usage that can be related to the outcome change. Likewise, it is hard to identify any other diagnostic change that could have had such effect on the outcome of these patients. We believe that the direct relation between TTI to the outcome measures was established by both the stratified effect in the different microbiological groups (e.g., contaminants vs. non-contaminants) and by including this variable in the multivariate model.

What can be the practical implications of our results, in light of these previous studies [17–21] The designation of a blood culture isolate as "contaminant" or "MDR" is a post-factum decision, which is not available to the laboratory upon initial gram-stain report, and hence, a practical benefit-analysis of RMI should be based on the initial report. Although the performance of RMI for all positive bacteria can offer many advantages in terms of timely treatment optimization, it seems that the highest clinical benefit of RMI might be in gram-negative bacteria. Since the majority of gram-positive bacteria in our institution were in fact contaminant, a more efficient strategy for us might just be to invest in reduction of contamination rate [22] rather than on RMI for all positive cultures. Future research should be focused on identifying specific clinical-epidemiological groups of patients that would benefit the most from RMI and other advanced diagnostic methods.

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Compliance with ethical standards

Conflict of interests The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the institutional Ethics Committee. Informed consent was not required as this was a retrospective, non-interventional study.

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