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ORIGINAL ARTICLE

Microbial identification and automated antibiotic susceptibility testing directly from positive blood cultures using MALDI-TOF MS and VITEK 2

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Abstract The study addresses the utility of Matrix Assisted Laser Desorption/Ionisation Time-Of-Flight mass spectrometry (MALDI-TOF MS) using VITEK MS and the VITEK 2 antimicrobial susceptibility testing (AST) system for direct identification (ID) and timely AST from positive blood culture bottles using a lysis-filtration method (LFM). Between July and December 2014, a total of 140 non-duplicate mono-microbial blood cultures were processed. An aliquot of positive blood culture broth was incubated with lysis buffer before the bacteria were filtered and washed. Micro-organisms recovered from the filter were first identified using VITEK MS and its suspension was used for direct AST by VITEK 2 once the ID was known. Direct ID and AST results were compared with classical methods using solid growth. Out of the 140 bottles tested, VITEK MS resulted in 70.7 % correct identification to the genus and/ or species level. For the 103 bottles where identification was possible, there was agreement in 97 samples (94.17 %) with classical culture. Compared to the routine method, the direct AST resulted in category agreement in 860 (96.5 %) of 891 bacteria-antimicrobial agent combinations tested. The results of direct ID and AST were available 16.1 hours before those of the standard approach on average. The combined use of VITEK MS and VITEK 2 directly on samples from positive blood culture bottles using a LFM technique can result in rapid and reliable ID and AST results in blood stream infections to result in early institution of targeted treatment. The combination of LFM and AST using VITEK 2 was found to expedite AST more reliably.

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Introduction

Sepsis is a medical emergency and timely initiation of antimicrobial therapy is vital for treatment. Institution of appropriate antibiotic therapy in the first hours has been reported to be associated with survival rates of 80 % and each hour of delay results in a decrease in survival by 7 % [1]. Significantly reducing the time to microbial identification (ID) and antimicrobial susceptibility testing (AST) is therefore critical for improving outcomes [2]. The standard protocol to diagnose bacterial sepsis involves blood culture preferably in a commercial automated blood culture system using liquid growth medium and overnight incubation of agar medium subcultures from positive bottles until colonies are visible prior to identification and susceptibility testing. By the time this is normally achieved, 36–72 h are consumed. The advent of Matrix Assisted Laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS), a technology based on protein fingerprinting, has successfully reduced the time to ID of pathogens in clinical microbiology laboratories [3]. By virtue of its high diagnostic accuracy MALDI-TOF MS is an attractive option to be used for direct detection of pathogens from clinical specimens. Recently, protocols for the direct ID of micro-organisms from positive blood cultures using MALDI-TOF MS have been developed without prior time-consuming subculturing. This has shown that a lysis-filtration method (LFM) has the potential to further decrease the time for ID of micro-organisms as well as susceptibility testing by almost 50 %, thereby paving the way for rapid initiation of appropriate antibiotic therapy in sepsis patients [4–6].

The aim of the present study was to utilize MALDI-TOF MS using VITEK MS (bioMérieux , Durham, NC) for direct identification and VITEK 2 for AST (bioMérieux, Durham, NC) from positive blood culture bottles after LFM. The objectives were to analyze the accuracy and to measure the turn-around time (TAT) for ID as well as AST of this assembly of assays, in comparison to our routinely used method of performing the ID and AST.

Material and methods

This study was performed at the department of Clinical Microbiology and Immunology at Sir Ganga Ram Hospital (SGRH), a 650-bed super-speciality hospital in New Rajinder Nagar, New Delhi between July and December 2014 after being approved by the IRB of the hospital (EC/07/14/687, dated 5.7.14). As the study involved analysis of cultured bacterial isolates and the results of the study were not to be used for patient management, requirement for consent was waived. Between July and December 2014, 140 positive blood culture bottles from 140 different patients were subjected to direct ID and AST by combined use of VITEK MS and VITEK 2 after LFM. Only mono-microbial cultures were studied.

Direct ID and AST testing from positive blood culture broths

Blood samples were cultured in non-charcoal containing aerobic (BacT/ALERT FA Plus), anaerobic (BacT/ALERT FN Plus), or pediatric aerobic (BacT/ALERT PF Plus) blood bottles on the BacT/ALERT–3D automated blood culture system (bioMérieux, Durham, NC) according to manufacturer's recommendations. Blood culture bottles signaling positive were removed from the BacT/ALERT–3D system, an aliquot was taken for Gram staining and sub-culture on solid media. Isolates grown from such culture media were used for classical ID and AST using VITEK MS and VITEK 2 (bioMérieux, France) as being representative of our routine protocol. Further, an aliquot was taken from the same positive blood culture bottles and processed using the LFM for direct ID by VITEK MS and full panel AST by VITEK 2 (Fig. 1). Full panel AST is the technique that we tested here for the first time in India to decrease TAT since VITEK 2 is normally used for

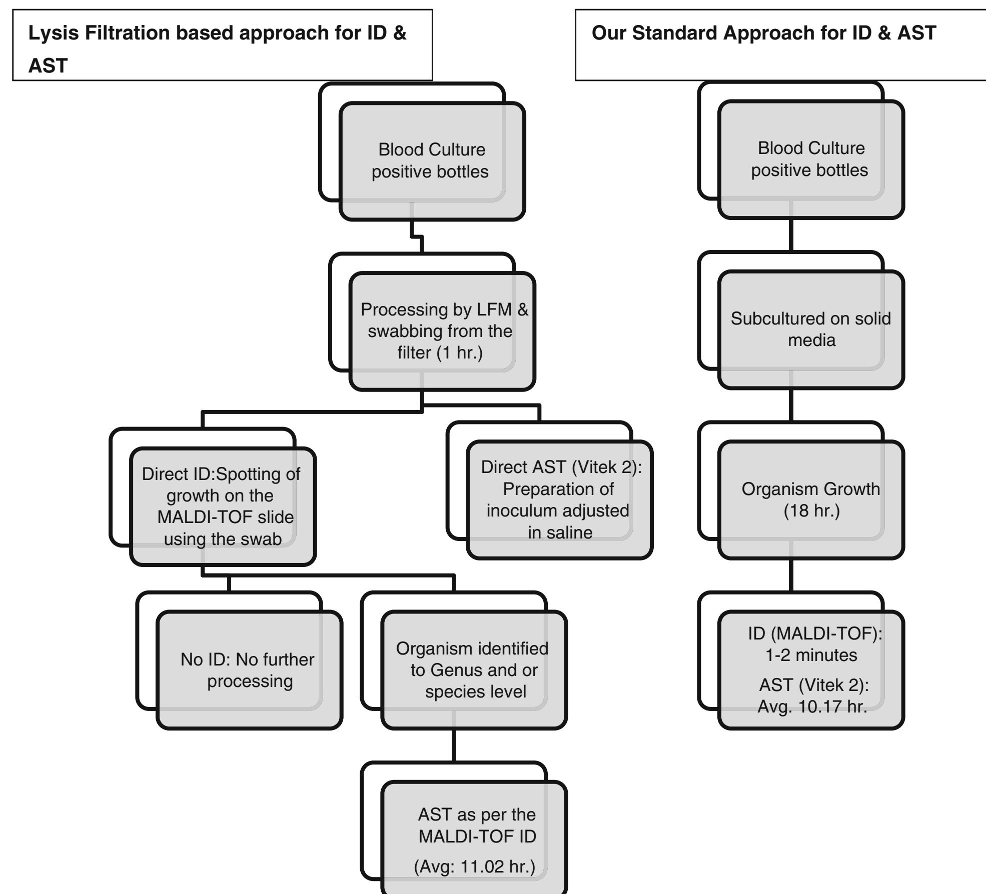

Fig. 1 Flow chart for identification and antimicrobial susceptibility testing of organisms obtained directly from positive blood culture bottles

Table 1 Direct identification results from positive monomicrobial culture bottles in studies using lysis-filtration method (LFM)

Sample	Present study	Fothergill et al. [5]	Machen et al. [6]	Rand et al. [10]	Farina et al. [11]
Total bottles	140	225	100	151	765[b]
Bottles with correct species ID by MALDI-TOF MS	84 (60 %)	176 (78.2 %)	94 (94 %)	137 (91 %)	538 (70.2 %)
Bottles with correct genus only ID by MALDI-TOF MS	15[a] (10.7 %)	4 (1.7 %)	2 (2 %)	5 (3.3 %)	4 (0.5 %)
Bottles with no ID by MALDI-TOF MS	37 (26.4 %)	40 (17.8 %)	3 (3 %)	8 (5.3 %)	138 (18 %)
Bottles with incorrect ID by MALDI-TOF MS	4 (2.9 %)	5 (2.2 %)	1 (1 %)	1 (0.66 %)	14 (1.8 %)

[a] Included 13 isolates of Salmonella spp.

[b] Included 48 bottles with mixed cultures and 23 with negative cultures

standard routine identification and susceptibility testing from the colonies grown on solid media.

LFM and direct identification by MALDI-TOF MS using VITEK MS

The lysis-filtration protocol for ID as previously published by Fothergill et al. [5] was used. Briefly, 2 ml of blood culture broth taken from positive blood bottles was added to 1.0 ml of lysis buffer (0.6 % polyoxyethylene 10 oleoyl ether [Brij 97] in 0.4 M [3-(cyclohexylamino)-1-propane sulfonic acid] [CAPS] filtered through a 0.2-μm-pore-size filter, pH 11.7), vortexed for 5 seconds, and allowed to incubate for 2 to 4 minutes at room temperature. The resulting lysate was filtered through a 25-mm filter of pore-size 0.45-μm for 40 seconds. The micro-organisms remaining on the filter were washed three times with wash buffer (20 mM Na phosphate, 0.05 % Brij 97, and 0.45 % NaCl filtered through a 0.2-μm-pore-size filter, pH 7.2), washed three times with de-ionized water, and removed from the surface by scraping the filter with a micro-swab.

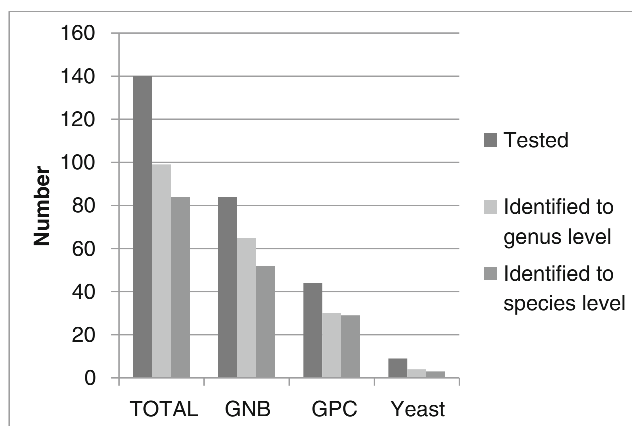

Fig. 2 Identification of organisms from blood culture broths using MALDI-TOF MS

Microorganisms swabbed and recovered from LFM filter paper were directly applied to VITEK MS target slides in duplicate, and were covered with 1 μl of CHCA matrix. For yeasts seen in the Gram stain, the dried micro-organism spots were first overlaid with 0.5 μl formic acid before the addition of matrix. The slide was run in the VITEK MS system using the MALDI-TOF MS research use only (RUO) system with the SARAMIS™ database and also the MALDI-TOF MS in-vitro diagnosis (IVD) MYLA database of bioMérieux. A bottle was considered to have a valid VITEK MS ID if at least one spot on the target slide gave a confidence level of ≥75 % [6] in at least one of the two databases without conflicting identifications from replicate spots of the same sample.

Antimicrobial susceptibility testing by VITEK 2

Using the same LFM membrane swab that was used for ID, a suspension was also made and set aside to be used for AST once the ID was known from the VITEK MS. The suspension was adjusted to a McFarland standard of 0.5–0.63 for Gram positive and Gram negative bacteria and used for direct AST on the VITEK 2 System. VITEK 2 cards were chosen according to the ID result given by the VITEK MS and were inoculated following manufacturers instructions. The ID from VITEK MS was introduced into the VITEK 2 system using MYLA to avoid any analytical errors and we used recommended criteria only. The resulting MIC was translated into clinical categories of susceptible, intermediate, or resistant following the Clinical and Laboratory Standards Institute (CLSI) recommendations [7]. The direct AST results were compared with the routine methodology (gold standard) and expressed as category agreement, very major error (false susceptibility), major error (false resistance), or minor error (intermediate versus susceptible or resistant).

The final ID and AST results in the hospital clinical laboratory records were used for comparison.

Table 2 Direct identification of all organisms

Organism	Number of isolates analysed	Correct ID by LFM and MALDI-TOF MS
Gram negative	87	65
E. coli	18	18
K. pneumoniae	22	18
Enterobacter spp	1	1
Salmonella spp	16	13
Salmonella typhi	4	2
Salmonella paratyphi A	1	1
Morganellamorganii	2	2
Proteus mirabilis	1	1
Serratiamarcenens	1	1
Pantoeaagglomerans	1	0
Acinetobacterbaumanii	10	6
Pseudomonas aeroginosa	2	0
Stenotrophomonasmaltophila	3	0
B. cepacia	1	0
Pasteurellamultocida	1	1
Ochrobacteriumanthropii	1	1
Chryseobacterium	1	0
Ralstonia spp.	1	0
Gram Positive	44	30
Staph epidermidis	9	4
Staph haemolyticus	5	3
Staph hominis	6	5
Staph capitis	1	1
Staph aureus	3	1
E. faecalis	5	4
E. faecium	8	6
Strept. vestibularis	2	2 (1 genus only)
Strept. oralis/ mitis	1	1
Strept. pneumoniae	1	0
Micrococcus luteus	3	3
Yeasts	9	4
C. albicans	1	1
C. auris	1	1
C. parapsilosis	2	2 (1 genus only)
C. tropicalis	2	0
C. glabrata	1	0
C. pelliculosa	1	0
C. lusitaniae	1	0
Total	140	99

Statistical analysis

The average turn around time for ID and AST using the combined LFM and VITEK 2 method was statistically compared to that of our standard routine method using Student's t-test. A p-value of <0.05 was considered statistically significant. All statistical tests were two-tailed.

Results

Direct microorganism identification from positive blood culture broths using LFM

Of the 140 positive mono-microbial blood culture positive bottles tested, there was agreement in 99/140 (70.7 %) for

Table 3 Comparison of direct susceptibility testing of bacteria using lysis-filtration method (LFM) with the standard approach

Organism	Number of isolates	Correct ID	Antimicrobials tested	Agreement with standard, n (%)	Minor error, n (%)	Major error (false R), n (%)	Very major error (false S), n (%)
Gram negative	78	65	737	708 (96.01)	21 (2.87)	4 (0.56)	4 (0.56)
E. coli	18	18	251	242 (96.4)	8(3.2)	0	1(0.4)
K. pneumoniae	22	18	250	242 (96.8)	6 (2.4)	1(0.4)	1(0.4)
Enterobacterspp	1	1	14	14 (100)	0	0	0
Acinetobacterbaumanii	10	6	66	61 (92.5)	3(4.5)	1 (1.5)	1 (1.5)
Salmonella spp	21	16	80	78 (97.5)	2(2.5)	0	0
Morganellamorganii	2	2	24	22 (91.8)	1 (4.1)		1 (4.1)
Proteus mirabilis	1	1	12	9 (75)	1 (8.4)	2 (16.6)	0
Serratiamarcenens	1	1	14	14 (100)	0	0	0
Pasteurella spp	1	1	12	12 (100)	0	0	0
Ochrobacteriumanthropii	1	1	14	14 (100)	0	0	0
Gram positive	40	27	154	152 (98.7)	1 (0. 65)	1 (0. 65)	0
Staph epidermidis	9	4	28	27 (96.4)	1 (3.6)	0	0
Staph haemolyticus	5	3	21	21 (100)	0	0	0
Staph hominis	6	5	35	35 (100)	0	0	0
Staph capitis	1	1	7	7 (100)	0	0	0
Staph aureus	3	1	7	7 (100)	0	0	0
E. faecalis	5	4	20	19 (95)	0	1 (5)	0
E. faecium	8	6	30	30 (100)	0	0	0
Strept. vestibularis	2	2	4	4 (100)	0	0	0
Strept. oralis	1	1	2	2 (100)	0	0	0
Total tested for AST		92	891	860 (96.5)	22(2.5)	5 (0.55)	4 (0.45)

organism identification using LFM directly and that from solid growth. Organisms could not be identified from 37 (26.4 %) bottles and 4 (2.9 %) bottles yielded incorrect results (Table 1). For the 103 bottles where identification was possible, there was agreement in 97 (94.17 %) isolates using both techniques. Overall, 99 (70.7 %) organisms were identified to the genus level and 84 (60 %) were identified to the species level (13 isolates identified as *Salmonella spp.* could not be speciated further and one isolate each of *Streptococcus vestibularis* and *Candida parapsilosis* were identified only up to the genus level using LFM). The ID results of the 87 Gram negative bacilli- (GNB), 43 Gram positive cocci- (GPC) and 10 yeast-positive bottles can be seen in Fig. 2. MALDI-TOF MS using LFM reported the correct identification for Enterobacteriaceae in 85.1 % (57/67), other GNB 40 % (8/20), *S. aureus* 33.3 % (1/3), Coagulase negative

Table 4 Susceptibility errors in the direct approach in comparison with other studies using lysis-filtration method (LFM)

Organism	Present study (1 %)		Machen et al. [6]; 2014 (3 %)	
	Major error (false R)	Very major error (false S)	Major error (false R)	Very major error (false S)
E. coli	0	1	1	0
K. pneumoniae	1	1	0	0
Acinetobacterbaumanii	1	1	0	0
Salmonella spp	0	0	–	–
Morganellamorganii	0	1	0	0
Proteus mirabilis	2	0	0	4
S. epidermidis	0	0	12	5
E. faecalis	1	0	0	0

Table 5 Comparison of time to antimicrobial susceptibility testing (AST) for direct identification (ID) between lysis-filtration method (LFM) and standard approach (hours)

Microorganism	LFM			Standard approach			P value
	Time to ID (h)	Time to AST (h)	Time to ID & AST (h)	Time to ID (h)	Time to AST (h)	Time to ID & AST (h)	
GNB	1	10.45	11.45	18	9.78	27.8	
GPC	1	12.41	13.41	18	11.1	29.1	
Total	1	11.02	12.02	18	10.17	28.2	<0.001

staphylococci 61.9 % (13/21), Enterococci 76.9 % (10/13) and Streptococci 75 % (3/4), respectively (Table 2). The incorrect identifications obtained included the following: an *E. faecium* was misidentified as *S. gallinarum*, one isolate each of *Acinetobacter baumanii* and *S. maltophila* were reported as *Mycobacterium kansasii* and one *S. typhi* was misidentified as *S. aureus*. However, the assays were not repeated a second time.

Direct AST using LFM and VITEK 2

For AST, a total of 891 bacteria-antimicrobial agent combinations were tested. Comparison of the direct AST results using LFM as inoculum with the AST from solid growth showed category agreement, minor error, major error and very major error for 860 (96.5 %), 22 (2.5 %), 5 (0.55 %) and 4 (0.45 %) combinations, respectively. There was category agreement in 708/737 (96.0 %) antimicrobials for GNB and 152/154 (98.7 %) for GPC (Table 3). Among the GNB, best direct AST results were seen for Salmonella spp., *K. pneumoniae*, *E. coli* and *A. baumanii*. For other GNB the microbial titers were low, so we could not comment on these tests. Overall, 98.9 % (882/891) of results for antimicrobials were either in agreement or were with minor error. A small number of major and very major errors (1 %) occurred in microorganisms such as *E. coli*, *K. pneumoniae*, *Acinetobacter baumanii*, *Morganella morganii* and *Proteus mirabilis* and *E. faecalis* (Table 4).

Time to identification and AST

The average time to obtain a final bacterial identification using the LFM method was 1 hour after the blood culture had signaled positive whereas in the standard approach, it took the additional time of at least 18 hours. The average time for AST using the LFM and that from classical solid growth was 11.02 h and 10.17 h, respectively. However, the average times required for a final bacterial identification and AST using the LFM approach as compared to the standard approach were 12.02 h and 28.2 h, respectively (Table 5), which was statistically significant ($P < 0.001$). Altogether, the results of direct ID and AST were available 16.1 hours earlier than that of the standard approach. Overall VITEK 2 AST results in combination with LFM were more encouraging than the alignment of LFM and VITEK MS.

Discussion

The ability to report identification and susceptibility results directly from positive blood cultures shortly after they signal positive for growth is of great value in reducing time to appropriate therapy. The study demonstrated the effectiveness of LFM combined with Vitek MS and Vitek 2 for identification as well as susceptibility testing of bacteria directly from positive BacT/Alert blood culture bottles. The organisms were correctly identified in 70.7 % cases in mono-bacterial blood cultures. Several groups have used mass spectrometry to identify microorganisms directly from blood cultures using different methodologies with varying success rates ranging from 74 % to 94 % [6, 8, 9]. Direct identification rates in various studies using LFM have been depicted in Table 1 [5, 6, 10, 11]. Fothergill et al. [5] could correctly identify 78.2 % of microorganisms using LFM. Much higher rates for identification (94 %) using LFM have also been reported by Machen et al. [6]. Lower rates of identification in our study could be explained by the fact that in both the studies mentioned above, reprocessing of bottles was done if “no identity” was generated in the first attempt. *In our study only a single attempt was made to identify the microorganism in order to define the performance of the method in a routine laboratory workflow.* It should also be noted that the transfer of the organisms from the filter to the mass spectrometry slide is learnt through experience and can be a likely source of inter-laboratory variations. Also, the remaining cell debris on the filter might lead to incorrect identification or no identification by the VITEK MS.

Higher rates of correct identification for GNB as compared to GPC were observed in our study which is similar to previously reported data [5, 12, 13]. Further, in our hands the process showed poor sensitivity in identifying yeasts, though the numbers tested (9 isolates) were low. Farina et al. [11] also reported that only one among eight yeast isolates could be correctly identified, possibly because yeasts might signal positive at low cell titres in automated blood culture systems [14].

Idelevich et al. [15] have also reported lower identification rates of 62.5 % for Candida spp. directly from positive blood cultures using MALDI-TOF MS. They also demonstrated that the Candida CFU/ml were significantly higher in positive blood culture broths with successful identification by direct MALDI-TOF MS. Future protocol modifications including higher volumes, an increased number of pellets and adding an extraction step may improve yeast identification results.

Although MALDI-TOF MS can be a useful tool for detection of antibiotic resistance in some cases, test methods are still evolving [16]. On the other hand, VITEK 2 is a highly standardized technique for AST. Our results demonstrate that VITEK 2 cards inoculated directly from positive blood culture broths using LFM showed a high degree of concordance with standard practice (>96 % both for GNB and GPC). Similar results for direct susceptibility using Vitek 2 have also been reported by Gomez et al. and Machen et al. [4, 6]. Also the combined use of LFM with VITEK MS and Vitek 2 has the advantage of using the same cells on the filter for both ID and AST testing, thereby minimizing the chances for sample mix-up. LFM resulted in 70.7 % correct ID results using VITEK MS in our hands which is lower than what is reported by other workers (Table 1) whereas it provided 96.5 % concordance for AST using VITEK 2. *Therefore, it appears that the combination of LFM and VITEK 2 worked more reliably than the combination of LFM and VITEK MS for ID*. In 14 positive blood culture broths where ID could not be achieved using LFM and MALDI-TOF, Vitek cards were inoculated on the basis of Gram stain of positive broths and direct AST was successfully performed with an overall category agreement of 96.1 % (data not included here), implying thereby that direct AST results could be made available to the treating unit to begin appropriate therapy even when the direct identification failed.

In our hands the major and VME in susceptibility recorded during the direct approach using LFM & Vitek 2 were low which has also been reported by Machen et al. using a similar approach [6] (Table 4). However, our errors in AST of *P. mirabilis* and *S. epidermidis* were much less. Paucity of data of this kind renders the current data to be difficult to evaluate. Further studies with larger numbers of isolates can provide a better insight in to the susceptibility errors of this newer methodology.

We found that the majority of results for blood cultures (both ID & AST) were obtained the same day the blood culture bottles signaled positive, 16.1 h earlier as compared to with the standard procedure. Also, with a category agreement of 96.5 % for the 891 bacteria-antimicrobial tested, this method can be used to report rapid AST results. However, in human resource constrained settings, to institute this technique round the clock may get labour intensive.

Our study had a few limitations. First, for direct ID from positive blood culture bottles, poly-microbial infections were not included and, second, due to its relatively small size, only a limited number of some important organisms such as *S. aureus* and yeast isolates could be studied. No anaerobic bacteria were isolated during the study period. However, positive blood cultures were tested in real time and the spectrum of organisms tested is representative of the mixture of blood culture isolates at our centre.

Conclusions

Our results show that the combined use of MALDI-TOF MS and Vitek 2 inoculated directly from positive blood culture bottles does provide an acceptable pathogen identification and susceptibility testing of common organisms in comparison to the standard protocol. The identification of yeasts is not encouraging using the current protocol. In fact, the combination of LFM and AST using Vitek 2 appeared to be more promising in providing AST reliably. Routine implementation of this approach provides correct results to the treating physician in more than 70 % of the bacteremic episodes and allows same day access to identification as well as AST results, potentially accelerating the institution of targeted antibiotic treatment. Further studies are needed to evaluate improvements in the patient outcomes and cost savings from adaptation of these new innovative approaches in clinical settings.

Compliance with ethical standards

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

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