The value of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry in identifying clinically relevant bacteria: a comparison with automated microbiology system

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Background: Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) has been developed as a new-type soft ionization mass spectrometry in the recent year. Increasing number of clinical microbiological laboratories consider it as an innovate approach for bacterial identification.

Methods: A total of 876 clinical strains, comprising 52 species in 27 genus, were obtained from Fudan University Affiliated Zhongshan Hospital. We compared the identification accuracy of the Vitek MS system (bioMerieux, Marcy l'Etoile) to other conventional methods for bacterial identification. *16S rRNA* gene sequencing was performed as a reference identification method in cases of discrepant results.

Results: The Vitek MS system consistently produced accurate results within minutes of loading, while conventional methods required several hours to produce identification results. Among the 876 isolates, the overall performance of Vitek MS was significantly better than the conventional method both for correct species identification (830, 94.7% *vs.* 746, 85.2%, respectively, P=0.000).

Conclusions: Compared to traditional identification methods, MALDI-TOF MS is a rapid, accurate and economical technique to enhance the clinical value of microorganism identification.

Keywords: Mass spectrometry; bacteria; identification

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Introduction

Rapid and accurate identification of pathogens is an important function of the clinical microbiology laboratory, particularly as it relates to choosing effective antibiotic therapies, reducing costs and shortening lengths of hospital stays. However, current bacterial identification methods are that are generally based on conventional phenotypic and biochemical methods usually require a significant time commitment ranging from four to twelve hours, in addition to higher consumable costs. Molecular methods are demonstrated to have complementary a value in bacterial identification, but not practical for routine use due to their associated complicated procedures and high cost levels.

As a result, matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS), a new-type soft ionization mass spectrometry method developed in the past several years, has been introduced for use by an increasing number of microbiology laboratories in multiple areas that include medical diagnostics, food quality control and environmental monitoring (1).

Materials and methods

Strains

We studied a collection of 876 non-repetitive isolates recovered from clinical sources including blood, urine, pus, sterile body fluid, and respiratory specimens received by our institution from July 2012 to March 2013. Among

those isolates, there were 270 enterobacteriaceae, 134 non-fermentative bacteria, 92 enterococci, 298 staphylococci, among which 217 isolates obtained from blood were coagulase negative staphylococci, 81 *staphylococcus* aureus, 70 *streptococcus* and 12 other bacteria.

Methods

Isolates were identified both by MALDI-TOF MS and conventional methods. In our routine workflow, an automated microbiology system was applied to identify the Gram-positive bacteria (BD PhoenixPID, panel448505), Gram-negative bacteria (BDPhoenixNID, panel448911) and streptococcus (BD PhoenixSID, panel448505). In cases where no identification result was achieved, the procedure was repeated to obtain a result. For *salmonella*, *Shigella spp*. and *legionella spp*., we chose serum plate agglutination, whereas for haemophilus influenza, the identification depended on the growing states in the plate added factor V and factor X. In cases where microorganisms could not initially be identified by MALDI-TOF MS due to reasons such as no presence of unique reference species, low mass spectra resolution, or simply no identification results, the samples were retested. When MALDI-TOF MS and the conventional method produced the same identification to the species level, the identification was considered final. In cases of discrepant results, partial *16S rRNA* gene sequencing was implemented to obtain final identification.

Devices

The following devices were applied in our research: (I) Vitek MS with IVD database V2.0 (BioMerieux, Marcy l'Etoile, France); (II) Phoenix System for bacterial identification and susceptibility (BD Company, Franklin Lakes, USA); and (III) Polymerase Chain Reaction Cycler (Applied Biosystems, Foster City, USA).

Reagents

The samples were cultured using a variety of medium types that are traditionally used in our practice, including blood plates (BioMerieux, Marcy l'Etoile, France), bacteria identification strips PMIC/ID, NMIC/ID and SMIC/ID (BD, Franklin Lakes, USA), Vitek MS-DS target plates and Vitek MS-CHCA matrix solution(BioMerieux, Marcy l'Etoile, France), 16s RNA primer (Sangon Biotech, China), Taq enzyme and PCR relevant reagents (Thermo Fisher Scientific, Waltham, USA).

Biochemical Identification

The Phoenix System for bacterial identification was used in accordance with the standard procedure recommended by the manufacturer.

MS identification

Pre-analytic preparation of samples was performed by using a sterile tip to pick bacterial colony isolates freshly grown on defined agar medium and then smearing a thin film onto a ground steel MALDI target plate. The dried microbial film was then overlaid with 1.0 μL α-cyano-4-hydroxycinnamic acid MALDI-TOF CHCA matrix. Then the sample-matrix mixture was dried at room temperature and subsequently inserted into the Vitek MS system for data acquisition. Quality controls were internally calibrated by using *Escherichia coli* ATCC8739 supplied by BioMerieux, which followed the same procedure aforementioned, with the exception of adding the clolnies to the calibration spot only. The data were processed automatically by the instrument software and the spectra were compared with reference libraries for bacterial identification matching.

16S rRNA identification

16S rRNA PCR and sequencing were performed after heat extraction of bacterial DNA. Polymerase chain reaction (PCR) was operated according to instructions by Hwang SM, *et al.*, 2011 (2), which included the amplification primer, reaction conditions and system. Then the PCR amplification products were delivered to the Liuhe Bejing Genomics Institute of Science and Technology Co., Ltd for sequencing, where gene sequences were compared using the BLAST website (http://blast.ncbi.nlm.nih.gov/Blast.cgi).

Statistic methods

Categorical variables were compared using Pearson's chi-square test of Fisher's exact chi-square test. Statistical significance was defined as ≤0.05 in a two-tailed test. All statistical analyses were performed using the SPSS 17.0 package.

Results

The 876 isolates contained 27 genus and 52 species. Using the BD Phoenix automated microbiology system, 746 isolates (85.2%) were correctly identified to the species level and 853 isolates (97.3%) to the genus level. In comparison, the Vitek MS system correctly identified 830 isolates (94.7%) to the species level and 866 isolates (98.9%) to the genus level (*Table 1*).

Of the 270 *Enterobacteriaceae* isolates, there was a significant difference (P=0.019) between the BD Phoenix automated system and the Vitek MS system for bacterial identification to the species level. The Phoenix system identified 258 isolates to the species level, whereas the Vitek MS system identified 243 isolates to the species level. A total of 27 isolates, accounting for 10% of *Enterobacteriaceae* isolates, could not be identified to the species level. A total of 16 isolates could not be distinguished between *Enterobacter asburiae* and *Enterobacter cloacae*, four *Shigella* isolates were misjudged to be *Escherichia coli*, four *Salmonella* isolates could not be resolved to the species level, and the remaining two *Enterobacter aerogenes* isolates were misidentified as *Enterobacter cloacae*. In the contrary, there was no significant difference identifying non fermentative bacilli when comparing the two species-level identification methods (P=0.769). Vitek MS correctly identified 129 nonfermentative bacilli compared to 127 by BD Phoenix. The misidentified results produced by Vitek MS included one *Burkholderia cepacia*, whose reference identification also consists of *Burkholderia vietnamiensis*, two *Achromobacter xylosoxidans*, which could only be identified to genus rather than species level, and one *ochrobactrum anthropi* which generated no result.

The VitekMS system proved far superior at identifying *Staphylococcus* species, correctly identifying 212 isolates (97.7%) out of 217 *Coagulase negative staphylococcus* compared to only 165 isolates (76.0%) by the Phoenix automatic microbiology system (P=0.000). Five isolates, four *Staphylococcus epidermidis* and one *Staphylococcus hominis*, failed to be identified accurately by Vitek MS. The Phoenix automatic microbiology system didn't yield species-level identification for a total of 52 isolates, including 30 *Staphylococcus epidermidis*, 12 *Staphylococcus hominis*, three *Staphylococcus haemolyticus*, one *Staphylococcus capitis*, two *Staphylococcus warneri*, one *Staphylococcus lugdunensis* and three *Staphylococcus cohnii*. In addition, two *Staphylococcus aureus* isolates were misidentified as *Coagulase negative staphylococcus*.

For both *Enterococcus and Streptococcus* species, there were also significant differences comparing the Phoenix system to the Vitek MS system, (P value =0.000, P value =0.007, respectively). A total of 92 *Enterococcus* isolates were successfully identified to the species level using Vitek MS, whereas the Phoenix system yielded 26 (28.3%) misidentifications. In addition, 22 *Streptococcus* isolates failed species-level identification using the Phoenix system, compared to 8 isolates using Vitek MS. Further details are shown in *Table 2*.

In addition, we summarized the strains which failed to be identified by Vitek MS for detail in *Table 3*. A total of 46 isolates were not in accordance with reference identification methods, among which 39 isolates (84.8%) were identified incorrectly to the species level but correctly to the genus level which we defined as minor error, and 7 isolates (15.2%) were identified incorrectly to the genus level which was defined as major error.

Discussion

Until recently, conventional methods for bacterial identification based primarily on biochemical and phenotypic techniques have prevailed in the clinical microbiological laboratory. All manual and many automated methods are time-consuming, and often require complex procedures and large amounts of biological material, which is particularly difficult to achieve for fastidious microorganisms with atypical biochemical characteristics (3). Molecular methods, including *16S rRNA* gene sequencing, have been demonstrated to have complementary value, but they are not practical for routine use due to their high cost and high burden on laboratory technicians. MALDI-TOF MS, a technology which is based on generating characteristic mass spectral fingerprints unique for each microorganism, has been proven as a more accurate and direct method for bacterial identification when comparing with conventional methods.

In our study, we focused on comparing the identification efficiencies for clinically common bacteria using the Vitek MS system and one conventional biochemical method offered in the BD Phoenix system.

Four MS target plates each containing 48 sample spots can simultaneously be loaded into the Vitek MS system for bacterial identification, achieving an identification result for each sample within an average of one to two minutes per sample. In comparison, the Phoenix system generally takes several hours to achieve identification results. Additionally, the Vitek MS system operates at much lower cost per sample volume compared to conventional methods.

Since MALDI-TOF MS was introduced to the clinical

Table 1 The comparison of identification results of bacterial isolates using Vitek MS and automated microbiology system

	No. of isolates	NO. of isolates with the indicated results using automated microbiology system		NO. of isolates with the indicated results using MALDI-TOF MS	
		Identification to the level of species	Identification to the level of genus	Identification to the level of species	Identification to the level of genus
Enterobacteriaceae	270	258	264	243	265
Escherichia coli	154	153	153	154	154
Klebsiella Pneumoniae	52	51	51	52	52
Enterobacter cloacae	16	15	16	0	16
Proteus mirabilis	9	9	9	9	9
Enterobacter aerogenes	6	6	6	4	6
Morganella morganii	7	7	7	7	7
Klebsiella oxytoca	2	2	2	2	2
Serratia marcescens	11	9	9	11	11
Serratia rubidaea	1	1	1	1	1
Citrobacter koseri	1	0	0	1	1
Citrobacter freundii	1	0	1	1	1
Enterobacter gergoviae	1	1	1	1	1
Shigella	5	2	5	0	0
Salmonella	4	2	3	0	4
Nonfermentative Bacilli	134	127	130	129	132
Acinetobacter baumannii	58	58	58	58	58
Pseudomonas aeruginosa	51	49	50	51	51
Stenotrophomonas maltophilia	6	5	5	6	6
Burkholderia cepacia	7	6	6	5	6
Pseudomonas alcaligenes	2	2	2	2	2
Acinetobacter junii	2	0	2	2	2
Elizabethkingia meningoseptica	2	2	2	2	2
Achromobacter xylosoxidans	2	2	2	0	2
Sphingomonas paucimobilis	1	1	1	1	1
Burkholderia multivorans	1	0	0	1	1
Chromobacterium indologenes	1	1	1	1	1
Ochrobactrum anthropi	1	1	1	0	0
Staphylococcus	298	244	295	293	296
Staphylococcus aureus	81	79	81	81	81
Staphylococcus epidermidis	101	71	98	97	99
Staphylococcus hominis	27	15	27	26	27
Staphylococcus haemolyticus	38	35	38	38	38
Staphylococcus capitis	30	29	30	30	30
Staphylococcus warneri	9	7	9	9	9
Staphylococcus caprae	3	3	3	3	3
Staphylococcus sciuri	3	3	3	3	3
Staphylococcus cohnii	5	2	5	5	5
Staphylococcus lugdunensis	1	0	1	1	1

Table 1 (*continued*)

Table 1 (*continued*)

	No. of isolates	NO. of isolates with the indicated results using automated microbiology system		NO. of isolates with the indicated results using MALDI-TOF MS	
		Identification to the level of species	Identification to the level of genus	Identification to the level of species	Identification to the level of genus
Enterococcus	92	66	91	92	92
Enterococcus faecalis	60	52	60	60	60
Enterococcus faecium	31	14	31	31	31
Enterococcus casselifavus	1	0	0	1	1
Streptococcus	70	48	68	62	69
Streptococcus agalactiae	6	6	6	6	6
Streptococcus anginosus	15	10	15	14	15
Streptococcus intermadius	2	1	2	2	2
Streptococcus constellatus	5	4	5	4	5
Streptococcus dysgalactiae	21	10	20	17	21
Streptococcus pyogenes	10	8	10	9	10
Streptococcus pneumoniae	11	9	10	10	10
Other bacterium	12	3	5	11	12
Aerococcus viridans	1	0	0	1	1
Micrococcus luteus	1	0	0	1	1
Corynebacterium aurimucosum	1	0	0	1	1
Microbacterium aurum	1	0	0	0	1
Corynebacterium jeikeium	5	3	4	5	5
Listeria monocytogenes	3	0	1	3	3
Total (%)	876	746 (85.2)	853 (97.3)	830 (94.7)	866 (98.9)

Table 2 Comparison of Phoenix and Vitek MS in identifying 864 isolates

	No. of isolates	No. of isolates identified to species level by			No. of isolates identified to: genus level by		
		Automated microbiology system	MS	P	Automated microbiology system	MS	P
Enterobacteriaceae spp.	270	258	243	0.019	264	265	1.000
Nonfermentative Bacilli	134	127	129	0.769	130	132	0.684
Staphylococcus spp.	298	244	293	0.000	295	296	1.000
Staphylococcus aureus	81	79	81	0.497	81	81	–
Coagulase negative staphylococcus (CoNS)	217	165	212	0.000	214	213	1.000
Enterococcus spp.	92	66	92	0.000	91	92	1.000
Streptococcus spp.	70	48	62	0.007	68	69	1.000
Total	864	743	819	0.000	848	854	0.236

Table 3 Isolates misidentified or unidentified by Vitek MS

Reference ID*	No.	Vitek MS	No.	Identification parameter	
				Minor error (%)	Major error (%)
Enterobacter cloacae	16	*Enterobacter cloacae/Enterobacter asburiae*	16	16	0
Enterobacter aerogenes	2	*Enterobacter cloacae/Enterobacter asburiae*	2	2	0
Shigella ssp	5	*Escherichia coli*	5	0	5
Salmonella typhi	2	*Salmonella group*	4	4	0
Salmonella enteritidis	1				
Salmonella choleraesuis	1				
Burkholderia cepacia	2	*Burkholderia cepacia/Burkholderia vietnamiensis*	2	2	0
Achromobacter denitrificans	2	*Achromobacter denitrificans Achromobacter xylosoxidans*	2	2	0
Ochrobactrum anthropi	1	*No identification*	1	0	1
Staphylococcus epidermidis	4	*Staphylococcus hominis*	2	2	0
		Staphylococcus capitis	1	1	0
		Staphylococcus haemolyticus	1	1	0
Staphylococcus hominis	1	*Staphylococcus epidermidis*	1	1	0
Streptococcus anginosus	1	*Streptococcus dysgalactiae*	1	1	0
Streptococcus constellatus	1	*Streptococcus anginosus*	1	1	0
Streptococcus dysgalactiae	4	*Streptococcus anginosus*	2	2	0
		Streptococcus pyogenes	2	2	0
Streptococcus pyogenes	1	*Streptococcus dysgalactiae*	1	1	0
Streptococcus pneumoniae	1	*no identification*	1	0	1
Microbacterium aurum	1	*Microbacterium flavescens*	1	1	0
Total	46		46	39 (84.8)	7 (15.2)

*, the identification result identified by *16S rRNA* gene sequencing is regarded as a reference ID for almost all the bacteria except for salmonella and Shigella, both of which refer to serum agglutination test.

microbiology laboratory, an abundant collection of literature (4,5) has highlighted many benefits that result from the use of this technology. In addition, the capability of MALDI-TOF MS to accurately identify bacteria to both the genus and species levels favors its potential application in almost all gram-positive bacteria and gram-negative bacteria in clinical practice (6,7). In our research, 94.7% isolates were correctly identified to the species level by MALDI-TOF MS. Our findings were consistent with a similar 92% correct identification ratio in 980 isolates studied by van Veen, *et al.* (8).

MS was remarkably better than the automated microbiology system in the identification of *Staphylococcus spp*. (P=0.000), especially for Coagulase negative staphylococci (CoNS), achieving 76.0% and 97.7% correct identification rates, respectively. CoNS strains were correctly identified (P=0.000) as similarly reported by of Dubois *et al.* (7). However, literatures estimating the value of Phoenix for identifying *Staphylococcus aureus* are still not in great number and differ significantly. Fahr *et al.* (9) had ever compared the Phoenix, Vitek MS and API ID32 Staph systems at the same time, which reached a concordance rate of 97.1%. On the contrary, Layer *et al.* (10) reported 27 reference isolates of *Staphylococcus aureus* for identification by MS. 18 isolates (66.67%) were correctly identified with a concordance rate of 66.67%, compared with a 76.19% concordance rate of the identification results for Staphylococcus epidermidis from clinical resource, which was in agreement with our finding. In Heikens's study of 47 CoNS isolates (11), 17 were misidentified and 2 failed to be identified, which showed a lower concordance rate.

The CoNS strains obtained in our study were all isolated from blood so it was particularly important to get accurate identification due the severity in clinical practice. Currently, CoNS strains are the most frequently detected strains in positive blood cultures, and there is no gold standard to

determine whether CoNS isolated from blood is pathogenic or contaminated. The U.S. Center for Disease Control and Prevention favors that it might present blood infection caused by CoNS if same strains were isolated from multiple bottles. Therefore, rapid and accurate methods able to identify CoNS to the species level can minimize unnecessary antibiotic regimens and reduce costs.

The occurrence of drug resistance of *Enterococcus faecalis* and *Enterococcus faecium* are rather different because the latter has a much higher drug resistance rate. As a result, correct identification to the species level plays a dominant role in monitoring therapy. Results from our study show that all the *Enterococcus spp.* were correctly identified by Vitek MS while only 17 (54.8%) isolates were correctly identified by the Phoenix system. For *Enterococcus faecalis* and *Enterococcus faecium*, using Vitek MS clearly offers a significant impact on the success of empiric antibiotic therapy and accuracy of statistical monitoring of bacterial resistance as compared to conventional methods.

In the context of difficult identification results of *Streptococcus spp.* with conventional methods, Phoenix has designed a dedicated plate to identify almost 30 strains of *Streptococcus*. Compared with 88.6% isolates of species-level identified by Vitek MS, the Phoenix system identified 68.6% in our study. Owing to its slow growing and small colonies, biochemical methods usually require more mature colonies, which subsequently leads to more time culturing purified colonies. However, a big advantage of Vitek MS, only one to two colonies are enough to do identification using Vitek MS, which allows it to offer accurate results to the clinician with a relatively rapid turn around time.

For the species-level identification of *Enterobacter cloacae* and *Enterobacter asburiae*, MALDI-TOF MS proved no real advantage over conventional methods, as also reported by others (12). Moreover, *Shigella*, belonging to *Escherichia coli* in genetics, has special virulence to humans (13). Thus, to avoid erroneous judgments, specimens of suspected *Shigella* and *Salmonella* infections, particularly from feces, need to be implemented by traditional biochemical methods and serum agglutination tests to obtain finalized results.

In addition to bacteria routinely found in our laboratory, we also identified some unusual ones which were not shown in *Table 1*, including *Haemophilus influenza*, *Legionella pneumophila*, *Clostridium difficile*, *Bacteroides fragilis*, and *Bacillus perfringens*. Among these isolates, the identification results of six *Haemophilus influenza* by Vitek MS accorded with the results of culture added in X and V factors. Several *Clostridium difficile* isolates and two *Legionella pneumophila* isolates identified by Vitek MS were all in agreement with results from standard methods. Therefore, we believe that Vitek MS might also be an effective identification method for some unusual bacteria. There are limitations of using Vitek MS, however. Mucoid bacteria, such as *Streptococcus pneumoniae* frequently failed to be identified. The most plausible reason for failed identifications for these species is the fact that it is quite easy to smear too much sample on the target spot.

In conclusion, the Vitek MS system represents a very powerful, high-throughput microbial identification technology that is efficient, rapid, relatively cheap, and easy to use. Compared with conventional methods, it can reduce workload and significantly shorten turn around times before delivering the formal reports to the clinicaians.

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