Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: MALDI-TOF Mass Spectrometry for Bacterial Species Identification: A Review of Diagnostic Accuracy and Clinical and Cost-Effectiveness

DATE: 21 April 2011

CONTEXT AND POLICY ISSUES

Matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) fingerprinting is a method used for the classification and identification of microorganisms, with applications in clinical diagnostics.[1] MALDI-TOF enables the analysis of molecules with higher masses, and mass spectrometry detects the mass-to-charge ratio of a bioanalyte, and provides bacterial spectra within minutes.[2] A database of known organisms is used to match the isolate under investigation, providing a matching score based on identified masses and their intensity correlation.[1] The method may be used to identify micro-organisms from different genera, species, as well as strains of the same species.[2]

Recent reports indicate that MALDI-TOF MS may be more successful in identifying bacteria and yeasts than standard biochemical tests. This has important implications for patient care and health care costs, as this technology can potentially impact the speed and accuracy with which infective bacteria are identified and correctly treated.

The capital costs of a MALDI-TOF mass-spectrometer can be substantial, with current purchase prices ranging from USD$150,000 to USD$850,000, depending on the model.[3] Annual maintenance costs are estimated to be about 10% of the purchase price[3]

The present review was undertaken to summarize the literature on the clinical effectiveness, diagnostic accuracy, and cost-effectiveness of MALDI-TOF MS technology in bacterial species identification, compared with conventional biochemical tests, with the aim of informing decisions regarding the adoption of this technology.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of using MALDI-TOF mass spectrometry for bacterial species identification?

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2. What is the diagnostic accuracy and reproducibility of MALDI-TOF mass spectrometry for bacterial species identification?

3. What is the cost-effectiveness of using MALDI-TOF mass spectrometry for bacterial species identification?

KEY MESSAGE

Compared with conventional biochemical tests used in a clinical laboratory setting, MALDI-TOF MS may be performed more quickly and may be more accurate in correctly identifying a wide spectrum of bacteria. Data on the relative clinical impact of MALDI-TOF MS are limited. Some economic data suggest that it may be less costly to identify isolates using MALDI-TOF MS than with conventional biochemical tests.

METHODS

A limited literature search was conducted on key resources including PubMed, EMBASE, The Cochrane Library (2011, Issue 3), University of York Centre for Reviews and Dissemination (CRD) databases Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2006 and March 22, 2011.

The study screening selection criteria are provided in Table 1

Table 1: Selection Criteria

Population	Samples collected from adult and pediatric populations
Intervention	MALDI-TOF MS used to identify bacteria and yeasts isolated from patient samples
Comparator(s)	Various automated and manual panels of biochemical tests to identify bacteria and yeasts (examples include but are not limited to Vitek, Phoenix, API)
Outcome(s)	Q1: Clinical Outcomes: acquisition rate, colonization rate, infection rate, turnaround times Q2: Diagnostic performance: sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, identification rates Q3: Economic evaluation outcomes
Study design	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations

SUMMARY OF FINDINGS

The literature search yielded 245 citations, as well as 38 references from the grey literature. Abstracts were reviewed and those indicating a comparative evaluation between MALDI-TOF MS and another method of bacterial identification were selected. Thirty-six comparative studies were identified and retrieved for further screening and final selection. Studies that involved biochemical testing but that were reported in abstract form, studies that did not clearly state the

comparator, or studies that included non-biochemical tests among several comparators, were excluded and have been listed in the Appendix. A total of nine studies[2,4-11] were included in this report, all of which were comparative laboratory experiments. There were no health technology assessments, systematic reviews, meta-analyses, or randomized controlled trials identified. Two studies[4,5] evaluated turn-around times, two [4,5] assessed the economic costs of MALDI-TOF MS, and seven studies[2,6-11] assessed the relative diagnostic accuracy of MALDI-TOF MS and biochemical testing.

Clinical Effectiveness

The only relevant measure of clinical effectiveness that was identified was turnaround time, which was reported in two studies.[4,5]

Cherkaoui et al.[4] (2010) compared the identification turnaround times of MALDI-TOF MS versus conventional biochemical tests (including rapid indole, rapid catalase, Pastorex Staph-Plus latex agglutination, coagulase, API, and Vitek) on 720 isolates of *E. coli* (n=216 isolates), *S. aureus* (n=55 isolates), and other bacteria (n=449 isolates). Isolates were obtained from a hospital bacteriology laboratory, which received its samples from both inpatient and outpatient settings. Two MALDI-TOF models were used, the Bruker Daltonik Microflex and the Shimadzu Biotech Axima. A specific definition of the limits of the turnaround time was not provided. Using conventional methods, the average turnaround times for the identification of *E. coli*, *S. aureus*, and other bacteria were 1 hour, 1 hour, and 24 hours, respectively (average of 15 hours per isolate). With the MALDI-TOS MS, the average turnaround times for high-confidence identifications (ie. isolate matching scores ≥1.7 with the Bruker and ≥70% with the Shimadzu) and for low-confidence identifications (ie. matching score<1.7 with the Bruker and <70% with the Shimadzu) were 0.08 hours (for n = 636 isolates) and 24 hours (for n= 84 isolates), respectively (average of 3 hours per isolate).

Seng et al.[5] compared delays in identification of 1660 bacterial isolates using API, Phoenix, Vitek, and MALDI-TOF MS. The MALDI-TOF MS model used was Bruker Daltonik Autoflex II. Isolates were obtained from blood, cerebrospinal fluid, pus, biopsy, respiratory tract, wound, and stool specimens. A delay was defined as the time between the deposit of bacteria on the MALDI-TOF plate by the technician and the time the identification was ready to be transmitted to the clinician. The definition of a delay for standard biochemical tests was not described. The resulting ranges in delays are given in Table 2:

Table 2: Delays for Isolate Identification Methods in Seng et al.[5]

Method	Delay (in minutes)
API system identification	1080-2880
Phoenix system identification and susceptibility test*	300-1200
Vitek system identification	300-480
Vitek system identification and susceptibility test	300-480
MALDI-TOF	6-8.5

*A susceptibility test determines the likelihood that a given antibacterial will be successful in inhibiting or killing a specific pathogen

Diagnostic Accuracy

Seven studies[2,6-11] reported comparative results on the diagnostic accuracy of MALDI-TOF MS versus conventional biochemical methods. Six of the seven MALDI-TOF mass spectrometers used in these studies were manufactured by Bruker Daltonik[6-11], and one was manufactured by Shimadzu Biotech.[2] Two comparators were used in five of the studies[2,6,7,9,10], and a single comparator was used in the remaining two.[8,11] Comparators included API[2,6,8-11], Phoenix[2,6,7], and Vitek.[7,9] Four studies looked at bacteria of a specific genus,[7,8,10,11] and three studies included several genera in their bacterial samples.[2,6,9] A summary of the studies' methods is given in Table 3.

Table 3: Summary of methods from studies reporting diagnostic accuracy of MALDI-TOF MS

Author (year)	MALDI-TOF MS model	Comparator(s)	Bacteria
Benagli et al.[2] (2011)	Shimadzu Biotech Axima	API, Phoenix	1019 isolates from >13genera, obtained from routine diagnostic labs
Bessède et al.[6] (2010)	Bruker Daltonik Ultraflex III TOF/TOF	API, Phoenix	1013 isolates from >20 genera, obtained from respiratory tract, ear, nose, throat, urine, biopsies, blood, pus, stools, genital tract, and other specimens obtained from hospital bacteriology laboratory
Dupont et al.[7] (2010)	Bruker Daltonik Autoflex	Phoenix, Vitek	234 coagulase-negative *Staphylococcus* isolates from 20 species, obtained from clinical microbiology laboratories
Martiny et al.[8] (2010)	Bruker Daltonik Microflex LT	API Campy	1689 isolates from *Campylobacter* genus, namely gastrointestinal pathogens obtained from hospital laboratories
van Veen et al.[9] (2010)	Bruker Daltonik Microflex	Vitek, API	980 isolates in 42 genera/92 species (including *Enterobacteriacae*, non-fermentative gram-negative bacteria, gram-positive cocci, and other miscellaneous bacterial organisms), obtained from blood, urine, pus, biopsy, swabs, cerebrospinal fluid, respiratory tract, and wound specimens obtained from microbiological laboratory.
Nagy et al.[10] (2009)	Bruker Daltonik Microflex LT or Ultraflex TOF/TOF	API Rapid ID 32A, API20	277 isolates from the *Bacteroides* genus, obtained in a clinical setting
Friedrichs et al.[11] (2007)	Bruker Daltonik Autoflex	API Rapid ID 32 STREP	99 isolates of *Viridans streptococci*, obtained from blood, abscesses, wounds, catheters, and cerebrospinal fluid.

MALDI-TOF MS: matrix-assisted laser desorption ionization-time of flight mass spectrometry;

All seven studies reported results on diagnostic accuracy at the species level.

One study[2] reported comparative sensitivity, specificity, positive predictive value, and negative predictive value. In each of the 11 species tested (705 isolates), MALDI-TOF MS sensitivity and negative predictive values (NPVs) were the same or higher than those obtained with Phoenix and API. Lowest sensitivity values were noted with *Enterobacter cloacae,* and highest were with *Pseudonomas aeruginosa*, with both identification methods. Specificity and positive predictive value was 100% with both methods. The results for sensitivity and NPV of the two diagnostic comparators in the eleven bacterial species are given in Table 4.

Table 4: Sensitivity and Negative Predictive Value of MALDI-TOF MS and API/Phoenix in 11 bacterial species from Bengali et al.[2]

Bacteria	MALDI-TOF MS		API/Phoenix	
	Sensitivity (%)	NPV (%)	Sensitivity (%)	NPV (%)
Acinetobacter baumanii	87.50	99.8	81.25	99.7
Enterobacter aerogenes	93.75	99.9	93.75	99.9
Enterobacter cloacae	69.44	98.9	30.56	97.5
Escherichia coli	95.58	98.2	90.82	96.4
Klebsiella oxytoca	79.17	99.5	62.50	99.1
Klebsiella pneumonia	90.57	99.5	58.49	97.8
Morganella morganii	93.33	99.9	93.33	99.9
Proteus mirabilis	98.67	99.9	96.00	99.7
Pseudonomas aeruginosa	99.17	99.9	97.50	99.7
Serratia marcescens	95.65	99.9	86.96	99.7
Stenotrophomonas malophilia	96.97	99.9	93.94	99.8

NPV:negative predictive value

A separate analysis of four species of *Staphylococcus* showed higher sensitivity values with MALDI-TOF MS than either API or Phoenix in three of the four species, and higher specificity with MALDI-TOF MS in all four.

The remaining six studies[6-11] reported comparative identification rates. None of the studies provided definitions of identification using biochemical test comparators. Three studies[6,9,10] defined identification at the species level using the Bruker MALDI-TOF MS as a score of ≥2.0 (range 0.0-3.0). Five studies[6-10] reported higher identification rates with MALDI-TOF MS, and one study[11] reported 100% identification rates with both MALDI-TOF MS and API.

Most authors concluded that MALDI-TOF MS was a favorable identification method.

The results of studies reporting diagnostic accuracy are summarized in Table 5.

Table 5: Summary of results from studies reporting diagnostic accuracy of MALDI-TOF MS

Author (year)	Diagnostic Accuracy	Authors' Conclusions
Benagli et al. (2011)[2]	MALDI-TOF identification rate in 1019 isolates: >98% Analysis of 705 isolates in 11 species (10 genera), with separate values obtained for	MALDI-TOF MS represents rapid, reliable, and cost-effective identification technique for clinically relevant bacteria.

Table 5: Summary of results from studies reporting diagnostic accuracy of MALDI-TOF MS		
Author (year)	**Diagnostic Accuracy**	**Authors' Conclusions**
	each species (range): (MALDI-TOF/API or Phoenix) Sensitivity: 69.4%-99.2%/ 30.6%-97.5% Specificity:100% all species, both methods PPV: 100% all species, both methods NPV:98.2% -99.9%/96.4% -99.8% (see Table 4 for details) Sensitivity and NPV values consistently the same or higher with MALDI-TOF for all 11 species. Separate analysis of 4 species of *Staphylococcus* showed higher sensitivity values with MALDI-TOF than either API or Phoenix in 3 of 4 species, and higher specificity with MALDI-TOF in all 4. Low sensitivity noted with *Enterobacter cloacae* with all methods	
Bessède et al.[6] (2010)	(MALDI-TOF/ Phoenix or API) Identification (species): 97.3%/93.2% Identification (genus): 99%/98% Authors noted that some bacteria were not identified by MALDI-TOF because they were not in the manufacturer's database or were present in insufficient numbers, and MALDI-TOF failed in a certain number of cases concerning anaerobic bacteria.	The performance of MALDI-TOF MS is very attractive considering its efficiency and rapidity, and is an important tool for bacteriological identification in a routine laboratory.
Dupont et al.[7] (2010)	(MALDI-TOF/Phoenix/Vitek) All results at the species level Identification: 93.2%/75.6%/75.2% Mis-identification: 1.7%/23.1%/13.7% Absence of result: 5.1%/1.3%/0.9% Low identification: 10.3% for Vitek only After excluding bacteria not in one or more of the three databases : Identification: 97.4%/79.0%/78.6%	The present study demonstrates the robustness and high sensitivity of the microbial identification database used with MALDI-TOF MS technology

Table 5: Summary of results from studies reporting diagnostic accuracy of MALDI-TOF MS		
Author (year)	**Diagnostic Accuracy**	**Authors' Conclusions**
	Mis-identification:1.3%/21.0%/10.3% Absence of result: 1.3%/0.0%/0.9% Low identification: 10.2% for Vitek only	
Martiny et al.[8] (2010)	(MALDI-TOF/API Campy/Vitek) Identification: *Campylobacter jejuni* ssp. *jejuni*: 100%/94.4%/89.6% *Campylobacter coli:*100%/73.8%/87.7% Other *Epsilobacteria:*90.9%/47.7%/0%	Among the three evaluated commercial systems, MALDI-TOF MS appears to be the method of choice for the identification of *Campylobacter* and related organisms.
van Veen et al.[9] (2010)	(MALDI-TOF/Vitek or API) Identification (genus): 98.8%/98.0% Identification (species): 92.0%/83.1% Major error*: 0.1%/1.6% Minor error†: 1.6%/1.4% No identification: 0.8%/0.5% No uniform result: 0.3%/not applicable MALDI-TOF had significantly higher Identification rate among gram-positive cocci in cluster (94.3% vs. 63.2%, p<0.01) and significantly higher minor error rate among *Viridans streptococci* (57.1% vs. 0%, p<0.01).	MALDI-TOF MS is a rapid, simple, inexpensive, and high-throughput proteomic technique for the identification of bacteria. It generally performs equally as well or better than conventional techniques, and performance can be significantly improved when more spectra are added to the database.
Nagy et al.[10] (2009)	Identification (species): MALDI-TOF: 270/277: 97.5% API: 23 of the 270 isolates correctly identified by MALDI-TOF were discrepant. The authors did not describe the outcome for the remaining 7 isolates with API.	The MALDI-TOF MS method provided accurate and fast species identification for the most frequently isolated human pathogenic anaerobic bacteria, with good discriminatory power for closely related species. Extension of the database to include other anaerobic bacteria of clinical importance will enhance the value of this methodology in routine clinical microbiology laboratories for species identification of anaerobic bacteria.
Friedrichs et al.[11] (2007)	Identification at the species level was 100% for MALDI-TOF and API	MALDI-TOF seems to be a rapid and reliable method for the identification of species of *Viridans streptococci* from clinical samples.

MALDI-TOF MS: matrix-assisted laser desorption ionization-time of flight mass spectrometry; PPV: positive predictive value; NPV: negative predictive value; ssp: subspecies. *Incorrect genus identification; †Incorrect species identification.

Cost-effectiveness

Cherkaoui et al.[4] reported the average cost per isolate identified with MALDI-TOF MS and with conventional methods. The costs were described as being the actual costs to the laboratory, but details were not specified. Using conventional methods, the costs were USD$0.20 per identification of *E.coli*, USD$1.50 per identification of *S. aureus*, and an average of USD$10.00 for identification of isolates of various other bacteria combined. High-confidence identifications with MALDI-TOF MS cost USD$0.50 per isolate, while low-confidence identifications cost $10.50 per isolate.

Seng et al.[5] reported the cost per isolate identification. Costs included specific consumables, salaries, and depreciation costs for the apparatus assuming 20,000 isolates were analyzed per year. Cost estimates were given in 2008 euros. The cost of MALDI-TOF MS isolate identification was found to be lower than each of its comparators. The result of this analysis is given in Table 6.

Table 6: Costs of Isolate Identification Methods in Seng et al.[5]

Method	Cost/isolate, €
API system identification	4.6-6.0
Phoenix system identification and susceptibility test	12.65
Vitek system identification	5.9-8.23
Vitek system identification and susceptibility test	10.38-12.71
MALDI-TOF	1.43

Seng et al.[5] also mentioned that each of the biochemical identification methods would require a medium level of training of personnel, while that of MALDI-TOF MS would require a low-to-medium level of training, suggesting lower resource use. However, the authors did not provide details on how they evaluated training requirements.

Neither of the economic studies related their costs to relevant outcomes, (example: cost per correct identification) or considered downstream costs of correct/incorrect identification.

Limitations

There was limited information on the clinical effectiveness of MALDI-TOF MS, and information on most of the clinical outcomes specified in the search criteria for this report could not be found.

While most studies included a wide range of bacterial species, one study that considered a wide range of bacterial genera and species noted a limitation in the lack of inclusion of sufficient anaerobic bacteria and Gram-positive aerobic rods.[9]

Bessède et al.[6] noted that some bacteria were not identified by MALDI-TOF MS because they were not in the manufacturer's database or were present in insufficient numbers, and MALDI-TOF MS failed in a certain number of cases of identification concerning anaerobic bacteria. Indeed, one study[7] reported that identification rates increased when isolates that were not included in any one of the comparators databases were removed from the samples. Database exclusions may have important implications in some cases. One manufacturer has issued a

safety update[12] relating to a bioterrorism-relevant bacteria that was not included in their database, which lead to its subsequent incorrect identification.

The criteria for identification were not always stated for one or both comparators.

Several authors concluded that MALDI-TOF MS was relatively rapid and/or inexpensive,[2,6,9,11] however these conclusion were not based on explicit data and should be interpreted with caution.

One economic assessment[4] did not appear to take into account the relative costs of capital equipment. It is unclear if either of the reviewed economic studies considered annual maintenance costs, which can be 8%-12% of equipment list price[3]. Neither study reported their costs in relation to clinical outcomes.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Two studies identified in this review indicate that MALDI-TOF MS has shorter turn-around times than conventional biochemical tests. Studies using a wide range of species of bacteria in their evaluations suggest better diagnostic accuracy with MALDI-TOF MS compared with conventional biochemical tests, however these studies have stated limitations. Further improvements can be made to MALDI-TOF MS identification rates with updates to system databases to include more bacteria and increase their applicability. Data from two economic evaluations that estimated the average costs of processing isolates suggest that MALDI-TOF is less costly than standard methods, however further economic analyses, particularly as they relate to outcomes, are needed.

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APPENDIX: Studies Excluded From Report

Abstracts

Bessède E, Angla-Gre M, Delagarde Y, Sep Hieng S, Ménard A, Mégraud F. MALDI Biotyper, experience in routine clinical bacteriology in a university hospital [Abstract]. Clin Microbiol Infect. 2010 Apr 12;16:S523. (Presented at 20th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); Vienna, Austria; 10 -13 Apr 2010).

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Multiple comparators including non-biochemical tests

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Comparator not described

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