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Q&A

Use of MALDI-TOF for Diagnosis of Microbial Infections

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Although mass spectrometry is making its mark on all facets of clinical laboratory medicine, arguably no field is witnessing its impact more than clinical microbiology. The application of MALDI-TOF mass spectrometry (MALDI-TOF MS) to microbial identification is revolutionizing clinical microbiology by providing rapid identification with minimal sample preparation at a potential savings in costs. Across the globe, the degree of implementation of MALDI-TOF MS varies markedly. In Canada, Australia, and much of Europe, MALDI platforms are in routine use in clinical microbiology, whereas the US Food and Drug Administration has yet to provide clinical clearance. In this Q&A, 4 experts from across the globe with first-hand experience implementing MALDI-TOF MS in the microbiology laboratory provide insight into what this technology can and cannot provide, what it takes to bring it in house, and what direction it takes us in the future.

The application of MALDI-TOF MS to the diagnosis of microbial infections has been touted as a revolution in clinical microbiology. However, no technology is without its pitfalls. Can you please describe what you feel are the greatest strengths and limitations of MALDI-TOF MS?

Gilbert Greub: When it is used to identify bacterial strains and fungi, the main strengths of MALDI-TOF MS are the rapidity of the technique (<10 min), its low cost in terms of reagents and technician processing time [<2 Euros (<2.8 US dollars) per identification] and its overall >95% accuracy at the species level. One of the most important limitations of this technique is its relatively low analytical sensitivity (about 10^5–10^6 bacteria/well). Thus, the accuracy of the identification is increased when the identification is done on a colony grown on agar or on a blood culture pellet, i.e., after a culture-based amplification step. Consequently, MALDI-TOF MS is not a tool currently suitable to detect a low amount of bacteria potentially present in physiologically sterile samples such as cerebrospinal fluids.

Susan Poutanen: The greatest strengths of MALDI-TOF MS include: (1) the fast turnaround time associated with its use for the identification of bacteria and yeast grown on standard culture media; (2) the cost savings in supplies and work load associated with its use compared to traditional identification methods; (3) the ability to incorporate MALDI-TOF MS into robotic automation in the laboratory; (4) the improvement on the work flow of the laboratory associated with having an earlier organism identification; (5) the improvement in patient care and antimicrobial stewardship associated with having an earlier organism identification; and (6) the potential for future applications, such as identification of filamentous fungi, identification of resistance mechanisms such as the production of carbapenemases, and assisting with epidemiologic typing.

The greatest limitations of MALDI-TOF MS include: (1) the up-front cost of purchasing a MALDI-TOF MS instrument; (2) lack of a comparable high-speed susceptibility system, which results in a substantial lag between having a reported organism and reporting its associated susceptibility results; and (3) the potential for technolo-

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gists to lose the skill set associated with identifying organisms by traditional means, which may result in errors when working in laboratories or sections of laboratories not using MALDI-TOF MS.

Jens Jørgen Christensen: In combination with speed, low costs, and ease of use, a major advantage of MALDI-TOF MS is that only highly probable identifications are provided by the scoring algorithms. If the system cannot generate an exact identification, no suggestions are provided, and, instead, low score values and warning comments are given, thereby minimizing false identifications. A limitation is that although the device is robust when examining bacterial strains from many different species, closely related species, such as *Streptococcus pneumoniae*, *S. mitis*, and *S. oralis*, may be difficult to separate. Preparation (extraction, growth) of strains, inclusion of species in the database, and the method used for creation of consensus mass spectra may act as both strengths and limitations; further standardization and optimization will be needed.

Markus Kostrzew: The greatest strengths of MALDI-TOF MS are its accuracy and speed, enabling a faster correct treatment of patients. Its main limitations, at least currently, include restricted application areas without prior culture and the discrimination of phylogenetically very closely related microorganisms (e.g., *Shigella*/*Escherichia coli*).

What do you feel are the major considerations (e.g., technical, economic) to include when implementing MALDI-TOF MS in the clinical microbiology lab? What reasons, if any, are there to hesitate in incorporating MALDI-TOF in the clinical laboratory?

Gilbert Greub: When a new tool is made available, it is important to consider the advantages and limitations of the technique and, more specifically: (1) when to use it; (2) how to use it; (3) how to interpret results; (4) how to ensure appropriate traceability of results; and (5) the controls and maintenance that are required. Regarding MALDI-TOF MS applied to clinical microbiology, this technology may be used to identify any strains considered to be clinically significant, when isolated colonies are available on agar, or when a blood culture is positive. Despite its high accuracy, interpretation of results obtained with MALDI-TOF MS is essential. This interpretation is largely influenced by the content and quality of the database, as well as by the identification algorithm. The traceability may be largely improved by using an automated colony-picking system and by an automated transfer of MALDI-TOF MS results to the laboratory information system. Due to the cost of the MALDI-TOF MS instruments [approximately 200 000 Euros (280 000 US dollars)] and of their maintenance [approximately 20 000 Euros (28 000 US dollars) per year], clinical microbiology laboratories identifying $<$5000 strains per year should opt for other, more cost-effective identification approaches. Another major point to consider when implementing MALDI-TOF MS in a routine diagnostic microbiology laboratory is the use of adequate controls, including negative and positive controls as well as a calibration controls. Internal and external controls should also be considered in the future.

Susan Poutanen: The major considerations when implementing a MALDI-TOF MS in the clinical laboratory should include: (1) the breadth and accuracy of the database and the ability for laboratories to be able to verify this; (2) the throughput of the instrument; (3) the ease of use of the instrument; (4) the mechanical reliability of the instrument; (5) the ability for the results of the instrument to be interfaced to a laboratory information system; (6) the best way to implement MALDI-TOF MS to maximize work flow efficiency throughout the laboratory; (7) the cost of the instrument; (8) the number of identifications typically performed in the laboratory and the associated length of time before the laboratory would expect to see a cost return on this investment; and (9) the optimal way to report identifications provided by MALDI-TOF MS to limit confusion that may be caused by reporting new species names—for example, key stakeholders should be consulted regarding their preference to have organisms that may have traditionally been reported with group-level identification (e.g., coagulase-negative staphylococci, viridans group streptococci, *S. anginosus* group) continue to be reported with group-level identification, despite species-level identification being available through MALDI-TOF MS.

There are some laboratories that may want to hold off in incorporating MALDI-TOF MS. Specifically, laboratories with small numbers of specimens need to weigh the benefits of MALDI-TOF MS against the limi-

tations and recognize that it will take longer for them to see the cost return of incorporating MALDI-TOF MS, compared to larger laboratories. It may be prudent for these laboratories to wait until the cost of MALDI-TOF MS instruments is reduced, as is expected in future years.

Jens Jørgen Christensen: On the assumption of an adequate validation process, economic considerations and laboratory work flows must be carefully examined and a cost–benefit analysis performed.

Communication of MALDI-TOF MS data to the clinicians is also of major importance. It will be important to incorporate MALDI-TOF MS data with other major characteristics used for grouping of bacteria. One must be mindful that reporting to clinicians is a question of useful communication—presenting newly published genus and species names must be balanced with the clinical value of such information. Additionally, laboratories must have a policy in place for how to deal with unfamiliar genera and species.

Markus Kostrzew: I don't see a reason to hesitate, but a laboratory must plan very well how the technology can be integrated into the general laboratory work flow. Integration into the existing laboratory information system is essential.

What do you feel are the most significant contributions that implementation of MALDI-TOF MS can make in the clinical microbiology laboratory?

Gilbert Greub: For the past 3 years, we have routinely used MALDI-TOF MS to identify microbial strains from a positive blood culture pellet. This has a major impact on clinical management and represents one of the most significant contributions of MALDI-TOF MS in clinical microbiology. Indeed, the bacterial identification may partly guide the antimicrobial treatment, improving, for example, by about 30% the adequacy of the empirical antibiotic regimen for gram-negative bacteremia. This may have a major impact on morbidity and mortality. MALDI-TOF MS also allows much faster identification of bacterial colonies present on an agar plate than commercial phenotypic systems, such as the VITEK.

Susan Poutanen: Given that many clinical microbiology laboratories are faced with an increasing work load and yet decreasing numbers of staff and healthcare dollars, the cost efficiencies of MALDI-TOF MS and potential for its incorporation into automation are the most significant contributions associated with the implementation of this technology into a clinical laboratory.

Jens Jørgen Christensen: Implementation of MALDI-TOF MS affords 3 significant contributions. First, there is the rapid identification of cultured bacterial strains and direct identification from positive blood cultures, which provide clinical guidance and permits optimal antibiotic treatment at least 24 h before what was possible with previous techniques. Direct identification of pathogens can be of great significance for the initial treatment of serious invasive infections. Second, with respect to identification of fastidious bacteria, MALDI-TOF MS requires only minute amounts of material, typically a fraction of a colony, thereby eliminating the need to inoculate multiple growth plates. Third, antibiotic-susceptibility testing and resistance-determinant testing are also within reach, which will provide information on, for example, methicillin susceptibility or carbapenemase production. This application, however, requires further investigation and standardization.

Markus Kostrzew: The implementation of MALDI-TOF MS in a clinical microbiology laboratory can reduce the work load of the staff by substituting many partially elaborate tests for the majority of isolates. The fast time to result enables the early reporting of microbial identification, which is appreciated by many physicians.

When implementing MALDI-TOF MS in the clinical microbiology laboratory, laboratorians have the choice of several instruments, each with their own testing algorithm. What do you feel is the likelihood of establishing a harmonized microbial database and algorithm for identification? Do you believe this would be advantageous?

Gilbert Greub: It might be advantageous to have a single harmonized microbial database. However, the most important issue is that users may also add spectrum from well-characterized bacterial strains and species in a common open-source, web-based database. Such addition of new strains to the database should be controlled and validated to avoid the addition of poor-quality spectra that may lead to misidentification. Harmonization of algorithm is not mandatory; on the contrary, it might be of value to implement several algorithms chosen by the end user, since some algorithms may be better suited to applications such as *Staphylococcus aureus* typing or for the identification of closely related bacteria such as streptococci, whereas others might be ideal for the identification at the species level, of corynebacteria for example.

Susan Poutanen: Given the current competitive nature of the manufacturers involved with selling MALDI-TOF MS instruments, I do not see harmonization of instruments or microbial databases a likely possibility, at least in the near future.

While harmonization would be advantageous from the point of view of knowing that the same organism will be identified the same way by any MALDI-TOF MS instrument and so a patient's results can readily be compared from one laboratory using MALDI-TOF MS to another, there are also disadvantages. Having a diversity of instruments acts as a buffer reducing the number of laboratories reporting a potential systematic error associated with using a single MALDI-TOF MS. For example, if a systematic misidentification occurs with a specific organism in only one MALDI-TOF MS instrument and if all laboratories used that system, all would make this error. However, the number of laboratories reporting this error would be minimized by having a variety of MALDI-TOF MS instruments/databases used. In addition, if only one MALDI-TOF MS instrument or database were used, it may take longer for systematic misidentifications to be detected by laboratories, since they will potentially see verification of their results from other laboratories reporting the same error and not recognize the error until a later time.

Jens Jørgen Christensen: Database and algorithm developments have largely been company driven. Having alternative algorithms may be beneficial to identify discrepancies. On the other hand, this will also complicate things. Taxonomy is developing fast, and the concept of "polyphasic taxonomy," where all kinds of information on microorganisms are integrated, raises a need for incorporating MALDI-TOF MS data into that strategy. Therefore, algorithms must be as objective as possible to meet the future realities of bacterial phylogeny. The future might well be a combination of current algorithms and the introduction of new ones. Whether these developments will be company driven or arise from the scientific community, only the future will show. A combination is desirable.

Markus Kostrzew: Harmonization across different vendors is not realistic. Different instruments have not only different algorithms but also different spectra formats that are proprietary. The raw spectra are the basis of any further analyses, and the extraction of information from these spectra (e.g., peak lists) is one of the most critical steps in mass spectrometry analyses.

To what extent do you believe MALDI-TOF MS will be used in the microbiology laboratory? Do you believe it to be competitive or even a replacement for current assays?

Gilbert Greub: MALDI-TOF MS has been used in our laboratory since 2009 to routinely identify all isolated strains, about 400 per week. This has been associated with a large decrease in the use of VITEK cards, which are now used for the identification of only 5% to 10% of isolates that are not identified by the MALDI-TOF MS or that are only presumably identified (low score or discrepancy of MALDI-TOF MS result with some characteristics of the isolate). Similarly, the need for 16S rRNA PCR and sequencing (previously used to identify selected strains not identified by routine approaches) has been reduced by half since the introduction of MALDI-TOF MS in our laboratory. Thus, MALDI-TOF MS has largely reduced the need of many alternative identification assays. However, despite the accuracy and low cost of MALDI-TOF MS, clinical microbiologists will still use some rapid, cost-effective phenotypic tests, such as catalase or indole, as a first-line identification tool or to confirm MALDI-TOF MS results.

Moreover, regarding other MALDI-TOF MS applications, such as typing and carbapenemase detection, mass spectrometry represents a cheaper and faster first-line method. However, MALDI-TOF MS will not completely replace current methods due to obvious limitations of the technique for some of these applications.

Susan Poutanen: Yes, I believe MALDI-TOF MS will be used in the microbiology laboratory, and I believe it will be competitive and will even replace traditional assays, at least in some areas of microbiology laboratories. In fact, it already has in some laboratories. And while smaller laboratories may not be able to justify purchasing a MALDI-TOF MS instrument now, once demand increases and prices drop, I suspect that many if not most laboratories will be using this technology in some capacity.

Jens Jørgen Christensen: MALDI-TOF MS has the potential to replace and/or complement conventional phenotypic identification for most bacterial strains examined in clinical microbiology laboratories. The great advantages of being able to look for the presence of bacteria directly from specimens and eventually of antibiotic-susceptibility testing put the methodology in a very central position.

Markus Kostrzew: MALDI-TOF MS has already replaced biochemical testing in many laboratories. There are hundreds of laboratories using the technology for identification, partially as the one first-line identification system. A combination of MALDI-TOF MS and molecular biology–based assays may replace most biochemical tests in the future.

What strategies do you recommend for quality control and standardization when implementing MALDI-TOF MS for microbial diagnostics?

Gilbert Greub: Of course, negative and positive controls should be systematically added to each run. Negative controls will monitor the rate of false-positive results, which may be due to drips, inversions, or the presence of residual proteins. Indeed, despite thorough cleaning of the MALDI microplate, about 0.1% of target plate spots cleaned as recommended with trifluoroacetate will still contain residues that generate mass spectra wrongly attributed to some species. In addition to negative controls, a calibration positive control should be run on a regular basis, at least once a day. An internal control that will check the amount of bacterial material deposited on the target plate might also be considered in the future, but it still needs to be developed. Finally, also warranted is an external quality control that will allow comparison of the performance of different diagnostic laboratories.

Susan Poutanen: Verification of MALDI-TOF MS manufacturers' claims should first be completed, as would be done for any new traditional identification system. The Cumitech 31A entitled "Verification and Validation of Procedures in the Clinical Microbiology Laboratory," published by the American Society for Microbiology Press in September 2009 and edited by Susan E. Sharp is an excellent resource to use as initial guidance. Disagreements should be arbitrated with a reliable reference standard, such as 16S rRNA sequencing. Thereafter, ongoing validation of the ability of the MALDI-TOF MS instrument to correctly identify organisms should be continued with the use of regular quality control organisms and external quality assessments.

Jens Jørgen Christensen: Concepts of quality assurance have to be implemented for MALDI-TOF MS to ensure quality of reporting. This means that bacteria from different taxonomic entities must be tested, and the results evaluated. On a daily basis, laboratories must ensure that the desired quality of interpretation and reporting to clinicians is followed. This includes ongoing training and, in many laboratories, establishing a group of "expert users" who can troubleshoot and provide guidance when needed. Additionally, the quality assurance testing has to focus on the reporting of results to clinicians. Although it may be tempting to report updated taxonomic suggestions or detect new taxonomic entities, it is necessary to be critical in reporting, as much confusion can result from "loose" identifications and reports.

Markus Kostrzew: One should use the quality controls recommended by the manufacturers. These controls should be included in every run. In a regular manner, additional controls should be run to check the overall performance. Target cleaning can easily be controlled by negative controls (spots with matrix only).

How does the use of MALDI-TOF MS in microbiology compare with current assays (e.g., economically, ease of use, level of training, ease of interpretation, efficiency)?

Gilbert Greub: MALDI-TOF MS is exhibiting a performance for bacterial identification equal to or even better than most of the alternative methods of identification. Despite the relatively high cost of the instrument and the need for regular maintenance, MALDI-TOF MS in microbiology is economically very competitive, being much cheaper than phenotypic approaches such as VITEK cards and PCR/sequencing, due to both the low reagent costs and the very low technician time of mass spectrometry. Moreover, this technology may easily be implemented in the laboratory, since the instrument is relatively straightforward to use and most results are easy to interpret. However, interpretation of MALDI-TOF MS results are nevertheless very important, and the microbiologist should at least check if the obtained results correspond to a bacterial species that is expected according to: (1) the growth characteristics (atmosphere or media), (2) the colony morphology, and (3) the gram-negativity or -positivity nature of the colony, when available. The interpretation also includes the plausibility of a given species in a given sample, as well as the difference in score values between the best and second-best match. A good knowledge of the database content and the algorithm hidden behind the score of course will also improve the quality of the interpretation of MALDI-TOF MS results.

Susan Poutanen: Compared to traditional assays, the use of MALDI-TOF MS is more economical, is easier to use, requires less training, is easier to interpret, and is more time and work flow efficient than traditional methodologies. All around, it makes sense that this technology replace traditional assays as the routine identification system used in laboratories, at least in some capacity.

However, this does not mean that traditional assays are defunct. Depending on the instrument and database being used, there may be organism identifications for which MALDI-TOF MS has challenges. If this is found after a laboratory's verification of the instrument or is reported in the literature as a problem, there may be traditional testing that will need to be continued alongside MALDI-TOF MS to help differentiate

different organisms that may be potentially misidentified by the MALDI-TOF MS instrument.

In addition, there may be work flow circumstances where abbreviated identification methods currently in place in some areas of the laboratory (e.g., the urine bench) are more efficient to continue rather than moving all analyses over to MALDI-TOF MS.

Finally, as a backup system, should the MALDI-TOF MS instrument malfunction, some laboratories may decide to keep traditional identification assays available and ready to use, given the cost associated with purchasing a second MALDI-TOF MS instrument as a backup.

Jens Jørgen Christensen: The relatively low cost for strain examination, with cost estimates of 1 Euro (1.8 US dollars) per identification, makes MALDI-TOF MS competitive compared to existing identification methods. However, laser stability is critical, since exchanging it is rather costly. For the routine clinical microbiology laboratory, the relative ease of use for the technicians makes it a desirable setup, although it is not without its pitfalls. It is necessary to invest time in operational training and in interpretation of results and reporting to clinicians. The need for training and retraining must not be underestimated.

Markus Kostrzew: MALDI-TOF MS is easy to use. Nevertheless, since this technology represents a deviation from the techniques commonly used in traditional microbiology laboratories, thorough training is recommended. Once implemented, the technology is straightforward in interpretation in most cases. The positive economic impact was one of the major factors for the quick spread in the laboratories within Europe. Even laboratories with 40–50 identifications per day see a cost reduction.

Currently, MALDI-TOF MS is unable to diagnose microbial infections directly from blood, and therefore prior culture of the microbial agent is required. Similarly, MALDI-TOF MS is limited in its ability to identify polymicrobial infections. Do you feel that MALDI-TOF MS will eventually be able to be used for these purposes? If so, what steps are necessary? If not, why?

Gilbert Greub: To date, most laboratories use MALDI-TOF MS on positive blood culture pellets. The analytical sensitivity of MALDI-TOF MS, however, precludes its direct use on paucibacillary clinical samples such as blood. To ideally save time from sampling of blood to positivity of blood culture warrants an alternative fast amplification step or requires further development in terms of analytical sensitivity of the MS instrument. Polymicrobial bloodstream infections are not consistently identified with current algorithms. However, with improved identification algorithms (i.e., subtraction of peaks of the best hit), identification of bacteria present in polymicrobial infections will be further improved in the future. Identification algorithms taking into account not only the presence/absence of peaks but also peak intensities will also significantly increase the discriminative power of MALDI-TOF MS.

Susan Poutanen: There are data to suggest that direct detection from urine specimens, at least in specimens associated with significant growth of pure cultures, is already feasible with MALDI-TOF MS without the need for prior culture, which makes the use of MALDI-TOF MS directly from specimens, urine and otherwise, a promising possibility. To make this promising application a reality requires more work to determine what, if anything, should be done to each specimen type as a pretreatment to remove leukocytes or other material that may interfere with protein profiles. Additional work would also need to be done to improve the analytical sensitivity of MALDI-TOF MS in detecting organisms in low numbers or in mixed populations. If these direct specimen-testing strategies fail, then direct identification from broth-enriched specimens requiring short incubations is a potential other strategy, which is supported by promising preliminary data.

Jens Jørgen Christensen: MALDI-TOF MS has been applied mainly to cultured bacteria. However, promising results have also been accomplished when performing analyses directly on certain kinds of clinical specimens. In prospective studies encompassing many different taxa, 60% to 80% of monomicrobial-positive blood cultures were correctly identified, mostly to the species level. Direct testing of urine samples have also been met with success. There may be a potential for recognizing polymicrobial infections, although data are limited. Developments in sample preparation, matrix composition, and analytical software may improve these aspects considerably in the near future.

Markus Kostrzew: The direct identification from blood is not realistic, since the detection limit of MALDI-TOF MS, which is working without amplification, is probably too high. For other specimens, such as cerebrospinal fluid, the direct identification of pathogens might become possible when the sample-preparation protocols and the analytical sensitivity of the measurement are improved. For polymicrobial infections, a first algorithm is available. This must be further validated and revised if necessary. The complexity of mixtures that can be unraveled will be limited, probably up to 3 different microorganisms in a mixture,

since specific signals will get lost due to suppression effects. Also, the relative abundance of an organism in a mixture will restrict its detection, e.g., to a minimum of 10% abundance in a mixture.

Do you have any additional comments or suggestions?

Gilbert Greub: In the future, the detection of some toxins or other virulence factors will likely be possible by mass spectrometry. However, most toxins are not detected, due to the relatively narrow range of molecular mass (<20 000 Da) detected with current MALDI-TOF MS instruments.

Susan Poutanen: At the same time that MALDI-TOF MS is an emerging technology being offered to microbiology laboratories, PCR–electrospray ionization/mass spectrometry is another emerging technology that is also being introduced. While each has its unique advantages and disadvantages, adopting them may not necessarily be mutually exclusive. These emerging technologies, along with the introduction of automation, make it an exciting time to be in the field of clinical microbiology. In a relatively short window of time, these novel technologies will likely lead to substantial change in traditional microbiology laboratories as we know them today.

Jens Jørgen Christensen: One interesting aspect is the use of mass spectrometry for sequence-based identification, which can be a supplement to the protein-based identification setup. Additionally, although the focus has been on the identification of bacteria, identification options for invasive fungal infections are increasingly being investigated, and in the future we may be able to add these microorganisms to the list of well-identified taxa. Likewise, the potential in susceptibility testing needs additional studies.

Markus Kostrzew: Currently, MALDI-TOF MS is mainly used for species identification in the clinical microbiology laboratory. Recent developments show that there is a very good chance for its expansion to areas, such as hygiene screening, detection of virulent strains, and detection of certain resistances. Thereby, MALDI-TOF MS may become a core technology in the microbiology laboratory.

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