MALDI-TOF MS and its impact on patient care

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MALDI-TOF Mass Spectrometry and its impact on patient care

Outline

• Briefly describe the technology
• Current use in pathogen identification in clinical microbiology (bacteria & yeasts)
• Direct use in blood cultures
• MALDI-TOF MS and total laboratory automation
• Future directions

No declarations or conflicts of interest
MALDI-TOF Mass spectrometry

Matrix Assisted Laser Desorption Ionisation Time Of Flight
MALDI-TOF Mass spectrometry
Matrix-assisted laser desorption ionisation- time of flight mass spectrometer.
Typical MALDI-TOF Mass Spectrum

Linear positive mode

~240 laser shots

~15-30 sec. per sample

Mass range: 2000-20000 Da

*Haemophilus influenzae*
# Evaluation of Platforms

## Table 1. Examples of Recent Evaluations of Matrix-Assisted Laser Desorption Ionization–Time of Flight Mass Spectrometry for Routine Bacterial Identification

<table>
<thead>
<tr>
<th>System</th>
<th>No.</th>
<th>Type</th>
<th>Period of Isolate Collection</th>
<th>Genus Level</th>
<th>Species Level</th>
<th>Country</th>
<th>Comparator</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruker Biotyper</td>
<td>1013</td>
<td>Bacteria</td>
<td>2 mo</td>
<td>99%</td>
<td>97%</td>
<td>France</td>
<td>Phoenix, API, Biochemical</td>
<td>[72]</td>
</tr>
<tr>
<td>Bruker Biotyper</td>
<td>468</td>
<td>Bacteria</td>
<td>3 mo</td>
<td>97%</td>
<td>92%</td>
<td>Japan</td>
<td>MicroScan, API, Phoenix</td>
<td>[73]</td>
</tr>
<tr>
<td>Bruker Biotyper</td>
<td>2781</td>
<td>Bacteria</td>
<td>1 mo</td>
<td>96%</td>
<td>85%</td>
<td>Australia</td>
<td>VITEK2, API, Biochemical</td>
<td>[74]</td>
</tr>
<tr>
<td>Vitek MS</td>
<td>767</td>
<td>Bacteria</td>
<td>6 wk</td>
<td>95%</td>
<td>87%</td>
<td>France</td>
<td>VITEK2</td>
<td>[8]</td>
</tr>
<tr>
<td>Bruker Biotyper</td>
<td></td>
<td>Bacteria</td>
<td>3 mo</td>
<td>96%/94%</td>
<td>93%/93%</td>
<td>Belgium</td>
<td>Bruker Biotyper compared to Vitek MS</td>
<td>[6]</td>
</tr>
</tbody>
</table>

*a* v1 system/v1.1 database.

*b* Prerelease version of v1.1 database.
Replacement of conventional identification tests

- Gram stain
- Oxidase; Catalase tests
- Latex agglutination tests
- Tube coagulase
- Dnase plates
- Bile Aesculin plate
- Gonocheck test
- Phadebact
- X and V factors
- Tributyrin test
- API Strips (except enterics)
- VITEK GNID and GPID cards
- Bordetella antisera
Implementation

• Fitted well with routine flow
• Straightforward calibration, target cleaning & maintenance
• Training – minimal
• Health and safety - minimal impact
• Time to identification reduced
• Less use of Reference laboratory / 16 S PCR
• New names.....
MALDI-TOF Mass spectrometry

Advantages

- Ability to identify the increasing numbers of micro-organisms
- Single colony only required
- Rapid turnaround time - minutes
- Minimal training & ease of use
- Cost-effective consumables
- Reproducibility
- Potential of direct use on clinical samples
- Databases can be expanded locally
- “Green” technology

Limitations

- Cost of instrument – initial outlay
- Does not provide antimicrobial susceptibility results
- Some closely related organisms not differentiated e.g. *Escherichia coli*/*Shigella* sp. & *Streptococcus mitis*/*oralis* and *Streptococcus pneumoniae*
- Machine failure
- Loss of “traditional” microbiology skills
- Requires database to be regularly updated
Tan KE et al., J Clin Micro 2012; 50: 3301-8

- Prospective evaluation, Johns Hopkins hospital laboratory
- “Maldi protocol” vs. “standard protocol”
- 2,214 specimens, various benches
- 952 isolates (824 bacterial & 128 yeast)
- Identifications 1.45 days earlier ($P<0.001$) than standard identification methods
- Projected savings consumables/labour costs 56.9% in 12 months
Methods used by participants to identify pathogens sent out in UK NEQAS General bacteriology scheme

- Gradual move from conventional methods to MALDI-ToF

Slide courtesy of Shila Seaton, UKNEQAS
Antimicrobial susceptibility testing and MALDI-TOF MS

• No direct identification of antimicrobial susceptibility

• Confirmation of identification of an isolate can infer inherent resistance patterns or intrinsic susceptibility
Overview of MALDI-TOF MS based resistance tests currently under investigation:

**MBT-STAR-BL Assay**
Functional assay monitoring β-lactamase activity; β-lactam antibiotics only

**MBT-RESIST Assay**
Incorporation of stable isotope labelled amino acids; in principle all antibiotics, most suitable for protein biosynthesis blocking antibiotics

**MBT-ASTRA**
Semi-quantitative growth assay using an internal standard; in principle all antibiotics

From: Sparbier K et al. Methods 104 (2016) 48-54


**MBT-RESIST Assay**, MALDI Biotyper-Resistance Test with Stable Isotopes Assay;

**MBT-ASTRA**, MALDI Biotyper-Antibiotic Susceptibility Test Rapid Assay
### Antimicrobial susceptibility testing and MALDI-TOF MS

<table>
<thead>
<tr>
<th>Organism</th>
<th>resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Klebsiella pneumoniae</strong></td>
<td>Incubation with Ertapenem for detection of CPE</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>Meticillin resistance detection by stable-isotope labelling amino acids</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>Oxacillin, Ciprofloxacin, Cefepime, Vancomycin Semiquantitative method (MBT-ASTRA software)</td>
</tr>
</tbody>
</table>

- **Sparbier K et al.** J Clin Microbiol. 2013; 51(11): 3741
- **Maxson T.** PLoS ONE 2017; 12(8): e0183899
Direct use of MALDI-TOF MS on positive blood cultures

- Blood culture usually triggers $\sim 10^7$/ml
- MaldiTOF limitation of detection $\sim 10^5$/ml
Direct use of MALDI-TOF MS on positive blood cultures: clinical impact

- 115 patient episodes positive blood cultures
- 73 (63.5%) Direct id by MALDITOF-MS
- 70/73 (95.9%) concordant result with subsequent culture
- 28/115 (24.3%) having the ID on Day 1 would have had clinical benefit

## Direct use of MALDI-TOF MS on positive blood cultures: clinical impact

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Number of cases (28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection of antimicrobial agents</td>
<td>11</td>
</tr>
<tr>
<td>Identifying source of infection/further investigation</td>
<td>11</td>
</tr>
<tr>
<td>Determining clinical significance</td>
<td>14</td>
</tr>
<tr>
<td>Infection Control Intervention</td>
<td>0</td>
</tr>
</tbody>
</table>

Direct use of MALDI-TOF MS on positive blood cultures

- 277 episodes bacteraemia (157 adult & 40 paed)
- 71% direct microbial ID obtained

<table>
<thead>
<tr>
<th></th>
<th>Contamination confirmed</th>
<th>Modification of treatment regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult (157)</td>
<td>8.9%</td>
<td>13.38%</td>
</tr>
<tr>
<td>Paediatric (40)</td>
<td>37.5%</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

Direct use of MALDI-TOF MS on positive blood cultures – antimicrobial stewardship

- 143/165 (86.7%) monomicrobial bacteraemia correctly identified at genus level.
- Gram stain: impact in 20.8%
- MALDI ID: modification empirical Rx in 35.1%
- MALDI ID: modification 16/27 (59.3%) of monomicrobial bacteraemia caused by AmpC-producing Enterobacteriaceae.
- Early appropriate broadening of the antibiotic spectrum in 31/71 (43.7%).

MALDI-TOF MS & Total laboratory automation (TLA)

Mutters et al. Ann Lab Med 2014; 34:111

• BD Kiestra™ TLA + MALDI-TOF Ms compared to conventional methods 219 BC isolates

• 30.6 hr faster pathogen identification

• 12% (24/200) antibiotic adjusted due to Early Id (no susceptibility testing)

Theparee et al. J Clin Micro 2018; 56: 1-8

• BD Kiestra™ TLA + MALDI-TOF MS for > 61000 urine samples

• Retrospectively assessed TAT’s before & after implementation

• Median TAT to organism ID MALDI-TOF MS from 21.33 h to 18.02h

• Median TAT to organism ID after TLA + MALDI-TOF-MS from 18.02h to 16.79h

• Impact on time to AST reports
Future directions

• MALDI-TOF MS has revolutionised the routine identification of bacteria & yeast isolated in clinical microbiology laboratories
• Accurate & timely ID impacts on patient management
• Direct use in clinical samples e.g. blood culture has impact on antibiotic prescribing as well as work of infection specialist
• Combination with total laboratory automation systems can further reduce TAT identification & thereby patient care.
• Further work required on AMS