A multi-center prospective evaluation of the new Filmarray Meningitis/Encephalitis panel for rapid PCR-based diagnostics

C. Ottiger¹, M. Naegele², D. Meinel³,⁴, M. Keller⁵, S. Mitrovic⁶, K. Rentsch⁶, M. Oberle¹, Ch. Noppen², R. Sutter⁷, S. Tschudin-Sutter⁸, V. Hinic¹, O. Dubuis², D. Burki⁵, A. Egli³,⁴

¹Clinical Microbiology, Cantonal Hospital Aarau; ²Clinical Microbiology, Viollier AG, Allschwil; ³Clinical Microbiology, University Hospital Basel; ⁴Applied Microbiology Research, University of Basel; ⁵Clinical Microbiology, Cantonal Hospital Lucerne; ⁶Clinical Chemistry, University Hospital Basel; ⁷Clinic for Intensive Care Medicine, University Hospital Basel; ⁸Infectious Diseases and Hospital Epidemiology, University Hospital Basel, all Switzerland

No conflict of interests!
High clinical impact of Meningitis and Encephalitis

- Meningitis and encephalitis is associated with
  - High morbidity\textsuperscript{1,2}
  - High mortality\textsuperscript{1,2}
  - Significant health care costs\textsuperscript{3}

- Rapid treatment is associated with improved outcome\textsuperscript{4,5}

- Current gap in diagnostics: Identification of the causing pathogen\textsuperscript{6}
  - Time-consuming (culture based)
  - Due to pre-treatment sometimes unsuccessful.

Filmarray: Mengititis/Enzephalitis panel

- Bacteria
  - *Escherichia coli* K1
  - *Haemophilus influenzae*
  - *Listeria monocytogenes*
  - *Neisseria meningitidis*
  - *Streptococcus agalactiae*
  - *Streptococcus pneumoniae*

- Viruses
  - Cytomegalovirus
  - Enterovirus
  - Herpes simplex virus 1
  - Herpes simplex virus 2
  - Human Herpes virus 6
  - Human paraechovirus
  - Varicella zoster

- Yeast
  - *Cryptococcus neoformans/gattii*

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22.04.2017
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**Most common pathogens for acute community acquired meningitis/enzephalitis**

**Missing shunt infections e.g. Staphylococcus aureus, CNS, P. acnes**
Aims

- Assess the diagnostic performance of a new broad panel PCR system
  - Limit of detection for pathogens
  - Detection of all pathogens included in the panel
  - Sensitivity and specificity
  - Determine the “real world“ time to result
Methods: Limit of detection

- Limit of detection
  - Serial dilution (1:10) of pathogens spiked into cerebrospinal fluid (CSF)

- Comparison with
  - Plating and determination of colony forming units
  - Microscopy
  - PCR detection
A general low limit of detection could be determined

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Filmarray ME</th>
<th>Microscopy¹</th>
<th>PCR assay</th>
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<tr>
<td>E. coli K1</td>
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<td>-</td>
</tr>
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<td>L. monocytogenes</td>
<td>200 CFU/mL</td>
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<td>-</td>
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</tr>
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<td>200 CFU/mL</td>
<td>7’500 CFU/mL</td>
<td>-</td>
</tr>
<tr>
<td>C. neoformans</td>
<td>10 CFU/mL</td>
<td>&gt;40 CFU/mL</td>
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</tr>
<tr>
<td>HSV1</td>
<td>100 TCID50/mL</td>
<td>-</td>
<td>30 GEq/mL</td>
</tr>
<tr>
<td>HSV2</td>
<td>pos</td>
<td>-</td>
<td>79 GEq/mL</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>55 TCID50/mL</td>
<td>-</td>
<td>Semi-quant. PCR</td>
</tr>
<tr>
<td>VZV</td>
<td>pos</td>
<td>-</td>
<td>120 GEq/ml</td>
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Methods: Comparison with Goldstandard

- Four different diagnostic laboratories
  - All accredited due to the ISO norm 17025

- Comparison of Filmarray Meningitis/Enzephalitis with
  - Laboratory internal gold standards
  - Culture based diagnostics for bacteria
  - Standard single-PCRs i.e. GeneXpert, real time PCR
Filmarray shows high sensitivity

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<td>Negative</td>
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<td>63 (21.7%)</td>
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- **Positive results:**
  - Filmarray 73/291 = 25.1%
  - Routine diagnostic 63/291 = 21.7%

CMV was not considered in this analysis, as this is not routinely tested in the laboratories.
Filmarray shows high sensitivity

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- **Sensitivity:** 100%
- **Specificity:** 95.8%
- Positive predictive value : 86.3%
- Negative predictive value : 100%

- *7/10 were confirmed by another test i.e. specific PCR or antigen test
- 3/10 were confirmed “false” positive
Trouble shooting: ID of false positive

Correct shaped melt curves

Not correct shaped melt curves

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Time to result is around 3h
Time to result is around 3h
Summary and conclusion

- High sensitivity with low limit of detection for pathogens
- Be aware of unspecific detections -> check the meltcurve

Advantages:
- Short hands-on-time in sample preparation
- Short assay turn around time, overall about 3h
- Assessment of the most common community acquired pathogens

Disadvantages:
- Diagnostic gaps for pathogens e.g. staphylococci for shunt infections
- No information on antibiotic resistance
- No quantification
- Costs
Acknowledgement

- PD Dr. Dr. Adrian Egli
- Dr. Vladimira Hinic
- Dr. Dominik M. Meinel
- Clarisse Straub

- Dr. Dieter Burki
- Dr. Melanie Keller

- Dr. Cornelia Ottiger
- Dr. Michael Oberle

- Dr. Olivier Dubuis
- Dr. Michael Naegele
- Dr. Christoph Noppen
Thank you for your attention…
Questions?

Adrian Egli, MD PhD
Clinical Microbiology
University Hospital Basel
Email: adrian.egli@usb.ch
http://www.labormedizin-uhbs.ch

Applied Microbiology Research
Department Biomedicine
University of Basel
http://www.appliedmicrobiologyresearch.net