Laboratory Diagnosis of Central Nervous System Infections in Children

R. Selvarangan. BVSc, PhD, D(ABMM).
Professor, UMKC-SOM
Director, Microbiology Laboratory
Children's Mercy Hospital
Kansas City, MO 64108

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Objectives

• Discuss the epidemiology of CNS pathogens in children

• Describe the laboratory test methods for CNS infections

• Identify strengths and weakness of molecular assays

• Outline strategies for test implementation and improved patient outcomes
Meningitis and Encephalitis

Definitions

- **Meningitis**
  - Inflammation of the meninges-
    - abnormal WBC in CSF with few or
    - no focal neurological findings or
    - brain abnormalities by imaging

- **Encephalitis**
  - Inflammation of the brain parenchyma with focal or global
    - neurological dysfunction regardless of meningeal involvement.
  - Altered mental status with two or
    - more minor criteria (fever,
    - seizures, focal neurological
    - findings, CSF WBC >5 cells/mm3,
    - abnormal brain imaging, EEG)
Meningitis & Encephalitis

- Rates are highest in infants and older adults
- Viral meningitis is most common while bacterial, fungal and parasitic causes are rare

<table>
<thead>
<tr>
<th>US</th>
<th>Meningitis</th>
<th>Encephalitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence/100K</td>
<td>4-30</td>
<td>3-7</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>70K</td>
<td>20K</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.4 to 11.4%</td>
<td>5.8 to 17.1%</td>
</tr>
<tr>
<td>Cost in billion (US$)</td>
<td>1.2</td>
<td>2</td>
</tr>
</tbody>
</table>

Polage et al JCM 2016
Bacterial Meningitis

• On average, bacterial meningitis caused about 4,100 cases and 500 deaths in the United States each year between 2003 and 2007.

• **Newborns:** Group B *Streptococcus*, *Streptococcus pneumoniae*, *Listeria monocytogenes*, *Escherichia coli*

• **Babies and children:** *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* type b (Hib), group B *Streptococcus*

• **Teens and young adults:** *Neisseria meningitidis*, *Streptococcus pneumoniae*

• **Older adults:** *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* type b (Hib), group B *Streptococcus*, *Listeria monocytogenes*

https://www.cdc.gov/meningitis/bacterial.html
Effect of Vaccine on Bacterial Meningitis in USA

Figure 2: Prevalence of bacterial meningitis in the USA attributable to Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis, Streptococcus agalactiae, and Listeria monocytogenes, 1986–2007.\(^{1,6,52}\)
Viral Meningitis

• Viral meningitis is the most common type of meningitis, an inflammation of the tissue that covers the brain and spinal cord.
• **Non-polio enteroviruses** are the most common cause of viral meningitis in the United States, especially from late spring to fall when these viruses spread most often.
• Other viruses that can cause meningitis are
• Mumps virus
• Herpesviruses, including herpes simplex viruses, and varicella-zoster virus, measles virus, influenza virus
• Arboviruses, such as West Nile virus, Lymphocytic choriomeningitis virus, Western Equine encephalitis, Eastern Equine encephalitis, Powassan virus, etc
Encephalitis

- More than 100 infectious causes
- Large proportion with immune or antibody mediated disease or unknown etiology despite extensive testing.
- Only one third confirmed
- Viral infections in Immunocompetent host- HSV, VZV, EV and arboviruses
- Local epidemiology and risk factors need consideration for test selection. Increased expenses in lab testing
DIAGNOSIS OF MENINGITIS & ENCEPHALITIS
Clinical Signs

• Meningitis symptoms: fever, headache, and stiff neck.
• Nausea, Vomiting, Photophobia, altered mental status
  – Only 44% patients had fever, neck stiffness and altered mental status. 95% of episodes were characterized by two of the four symptoms including headache

• In newborns and babies: irritable, vomit, feed poorly, or appear to be slow or inactive, bulging fontanelle or abnormal reflexes.

• Encephalitis - objective clinical evidence of cerebral or cerebellar dysfunction.
Laboratory Diagnosis

- CSF analysis: WBC count, Glucose and Protein levels
- CSF, Blood and Urine culture
- Biomarkers- procalcitonin or CSF lactate
- Nucleic acid amplification tests (NAAT)
- If Encephalitis is suspected- serology for arbovirus, non-infectious etiology, imaging, EEG
# CSF Findings

<table>
<thead>
<tr>
<th>Test</th>
<th>Bacterial</th>
<th>Viral</th>
<th>Fungal</th>
<th>Tuberculous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opening pressure</td>
<td>Elevated</td>
<td>Usually normal</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Leukocyte count</td>
<td>≥1000/μL</td>
<td>&lt;100/μL</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Cell differential</td>
<td><em>Mainly neutrophils</em></td>
<td><em>Mainly lymphocytes</em></td>
<td><em>Mainly lymphocytes</em></td>
<td><em>Mainly lymphocytes</em></td>
</tr>
<tr>
<td>Protein</td>
<td>Mild–marked increase</td>
<td>Normal–mild increase</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Glucose</td>
<td>Usually ≤40 mg/dL</td>
<td>Normal</td>
<td>Decreased</td>
<td>Decreased: may be &lt;45 mg/dL</td>
</tr>
<tr>
<td>CSF-serum glucose</td>
<td>Normal–marked decrease</td>
<td>Usually normal</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>Mild–marked increase</td>
<td>Normal–mild increase</td>
<td>Mild–moderate increase</td>
<td>Mild–moderate increase</td>
</tr>
</tbody>
</table>

Data from [Body, 1987; Tang, 1988; Arevalo, 1989; Fishman, 1992; Wubbel, 1998; Zunt, 1999.](#) 

*Henryys Clinical Diagnosis and Management by Laboratory methods 22nd ed*
CSF Gram stain & culture

• Gram stain- LOD $10^4$/ml. Sensitivity ranges from 10-93% depending on pathogen and severity
  • *S. pneumoniae* and GBS (60%-90%)
  • *L. monocytogenes* (10-35%)

• Culture- LOD $10^2$ to $10^3$ /ml. Sensitivity 60-90%
  • Decreases further within 1-4 hrs of antibiotic.
  • Blood culture- adds additional diagnostic value; *Listeria*
Utility of Viral Culture of Cerebrospinal Fluid

- Less than 0.1% recovered non-enterovirus or herpes virus in culture.
- **Viruses were recovered from 1270 (5.7%) of 22,394 viral cultures of CSF samples. The viruses isolated included 1249 (98.4%) EV, 16 (1.3%) HSV, 3 (0.2%) cytomegalovirus, 1 (0.08%) varicella zoster virus, and 1 (0.08%) adenovirus.**
- Among 929 samples also analyzed with PCR for enterovirus, only 4 were PCR-negative, culture-positive; for diagnosing HSV infection, cultures identified no specimens that PCR missed. The estimated cost for these viral cultures was $1.16 million.

West Nile Virus - serology
NAAT- FDA approved

- **Single/Duplex PCR**
  - Herpes Simplex Virus
    - Aries HSV, Amplivue HSV, Lyra HSV+VZV, Simplexa Direct HSV*
- **Enterovirus PCR**
  - Xpert EV*
- **Parechovirus PCR**
  - None

- **Multiplex Panel PCR**
  - FilmArray Meningitis /Encephalitis Panel

- *approved for CSF
DIAGNOSTICS: PLANNING AND IMPLEMENTATION

HSV
EV/PAR-A
BACTERIAL
FUNGUS
PARASITES
HSV Disease

• HSV infections: 1 million genital HSV infections/yr.

• Both HSV-2 and HSV-1 cause primary genital infections. Reactivation more common with HSV-2.

• HSV sero-positivity: 10-50% in different races and socioeconomic groups.

• Neonatal HSV: Incidence is 1 in 3000 to 20,000 live births (500-1000/yr).

• Infected intra-partum (83%), post-partum (14%) and in-utero (3%). Symptomatic within 2 weeks of life.

• Incidence of vertical transmission is higher in women with primary infection (50-80%) compared to reactivation disease (5%).

• Diagnosis: Clinical presentation with in 2-4 weeks of life.
Neonatal HSV - Presentation

• Disseminated disease (25%), CNS disease (30%) or localized disease in newborn-skin, eye, mucosa (SEM) (45%).

• CNS disease: Encephalitis, seizures, lethargy, irritability, poor feeding, temperature instability.

• Disseminated disease: Hepatitis, pneumonia, CNS involvement (60%-75%), DIC.

• SEM disease: sepsis like syndrome, vesicular lesions may appear late in disease.

• Mortality high in disseminated and CNS disease, especially if left untreated.
Neonatal HSV: Risk Factors

Corey et al NEJM 2009
Neonatal HSV - Evidence

• Most cases of neonatal HSV occur in mothers who acquired HSV 1 or 2 for the first time near term.

• HSV 1 accounts for 30-50% of neonatal HSV and >75% of cases from recently acquired genital HSV1 in mother.

• No data to indicate that suppressive antiviral therapy near term reduces risk of neonatal herpes.

• Skin or mucosal lesion may appear late in disease course or not at all. Common presentation include sepsis-like syndrome or new onset seizures.

• Acyclovir IV therapy: SEM disease 14 days; CNS or disseminated disease 21 days.

• IgM antibodies are not reliable for detection of HSV disease.

Corey et al NEJM 2009
HSV CNS disease - Diagnosis

• Rapid diagnosis is critical for patient management.

• CSF pleocytosis: 20-80 WBC, mononuclear cell predominance, proteinosis 300-1000 mg/dL

• Radiological finding: temporal lobe involvement

• Culture of CSF is insensitive.

• PCR is the gold standard for CSF testing: sensitivity (80-95%), high specificity. Blood may be an additional specimen type for testing.
HSV Encephalitis
Temporal Lobe Involvement
HSV Meningo-encephalitis
HSV Laboratory Diagnosis

• HSV grows readily from all muco-cutaneous and vesicular lesions.

• “surface cultures” from skin vesicles, mouth or nasopharynx, eyes, urine, blood, stool or rectum-

• Co-cultured cells: H&V mix (AGMK + MRC-5).

• PCR of CSF (gold standard) and Plasma (added value)

• Culture of skin lesions & PCR if desired

Red Book 30th Ed 2015
**HSV PCR**

- In few cases CSF may be negative initially or late in disease- repeat PCR if clinical suspicion is high

- Probability of a positive result by CSF PCR declines each day following 2 days of effective acyclovir IV therapy

- Repeat PCR during therapy (> 7 days)- positive PCR result indicates poor outcome.

- Positive test result in first 24 hour after birth may represent virus from maternal source
HSV PCR and Acyclovir Therapy

- Impact of a direct HSV (dHSV) PCR assay on the time to result reporting and the duration of acyclovir therapy for children with signs and symptoms of meningitis and encephalitis.

- A total of 363 patients with HSV PCR results from cerebrospinal fluid (CSF) samples were included in this retrospective analysis, divided into preimplementation and postimplementation groups.

- All CSF were HSV negative. >60% in both groups received Acyclovir therapy.

- Implementation of rapid HSV PCR testing can decrease turnaround times and the duration of unnecessary acyclovir therapy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-Imp</th>
<th>Post-Imp</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAT</td>
<td>23.6 hr</td>
<td>9.1 hr</td>
</tr>
<tr>
<td>Acyclovir Discontinuation (mean)</td>
<td>31.1 hr</td>
<td>14 hr</td>
</tr>
<tr>
<td>Duration of Acyclovir Rx (median)</td>
<td>29.2 hr</td>
<td>14.3 hr</td>
</tr>
</tbody>
</table>

Enterovirus- Aseptic Meningitis
<table>
<thead>
<tr>
<th>Traditional taxonomy</th>
<th>Current taxonomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polioviruses</td>
<td>Human Enterovirus A (HEV-A)</td>
</tr>
<tr>
<td>PV1-3</td>
<td>CAV2-8, 10, 12, 14, 16; EV71, EV76 EV89, EV90, EV91</td>
</tr>
<tr>
<td>Coxsackie A viruses</td>
<td>Human Enterovirus B (HEV-B)</td>
</tr>
<tr>
<td>CAV1-22, 24</td>
<td>CAV9; CBV1-6; E1-7, 9, 11-21, 24-27, 29-33; EV69, EV73-75, EV77-8, EV79-88, EV100-101</td>
</tr>
<tr>
<td>Coxsackie B viruses</td>
<td>Human Enterovirus C (HEV-C)</td>
</tr>
<tr>
<td>CBV1-6</td>
<td>CAV1, 11, 13, 17, 19-22, 24, PV1-3</td>
</tr>
<tr>
<td>Echoviruses</td>
<td>Human Enterovirus D (HEV-D)</td>
</tr>
<tr>
<td>E1-7, 9, 11-21, 24-27, 29-33</td>
<td>EV68, 70</td>
</tr>
<tr>
<td>Numbered enteroviruses</td>
<td></td>
</tr>
<tr>
<td>EV68-71</td>
<td></td>
</tr>
</tbody>
</table>

*Enterovirus taxonomy has been revised by the International Committee for Reassignment of enterovirus species and genera.*
Enteroviral Disease

- Enteroviruses are the most common cause of aseptic meningitis in children during the summer months.
- About 75,000 cases of aseptic meningitis. Common in children less than 1 year old.
- Febrile illness, aseptic meningitis, encephalitis, paralysis, myocarditis and neonatal enteroviral sepsis.
- Clinical symptoms mimic bacterial meningitis and septicemia
Summer: Aseptic Meningitis

• Individual serotypes exhibit variations in temporal patterns of circulation and associations with different clinical manifestations.

• *Echovirus* 9 and 30 are commonly associated with aseptic meningitis.

• group B coxsackieviruses: myopericarditis,

• coxsackie A24 and entrovirus 70 with acute hemorrhagic conjunctivitis.

• enterovirus 71 with neurological manifestations especially in SE Asia.

• coxsackie A16 with hand, foot and mouth disease.
Enterovirus - Surveillance 1970 – 2005

- Common serotypes (echovirus 9, 11, 30, 6 and coxsackievirus B5 accounted for nearly 50%)

- Children <1 were more commonly infected (44%)

- Summer-fall seasonality (78%)

- CSF was the most common specimen type, followed by respiratory and fecal specimens (50%, 27% and 14% respectively)

CDC: MMWR Vol 55/No. SS-8
Enterovirus- Laboratory Diagnosis

- Specimens: CSF, throat, rectal/stool, urine, blood.
- CSF pleocytosis: not reliable in children less than 60 days.
- Culture of CSF-Primary Human and monkey kidney, BGMK, RD (group A coxsackieviruses). MRC-5 have limited sensitivity, delayed TAT.
- Realtime RT-PCR of CSF: Rapid TAT, Standard of Care laboratory test method.
- FDA approved RT-PCR methods:
  - GenXpert- random access and rapid turn around time- can impact patient management; Inhibition due to blood tinged CSF have been reported.
- CSF and blood are likely to yield positive result; combination of both improves diagnostic yield.

Mulford et al JCM 2004; Sefers et al JCM 2009; Rittichier et al PIDJ 2005
OBJECTIVE: To determine the cost savings of routine enterovirus testing and identify subgroups of infants with greater potential impact from testing among infants 0 to 90 days old with fever.

RESULTS: Of the 257 unique studies identified and screened, 32 were completely reviewed and 8 were included. Routine enterovirus testing was associated with reduced hospital length of stay and cost savings during peak enterovirus season. Cerebrospinal fluid pleocytosis was a poor predictor of enterovirus meningitis. The studies were all observational and the evidence was of low quality.

CONCLUSIONS: Enterovirus polymerase chain reaction testing, independent of cerebrospinal fluid pleocytosis, can reduce length of stay and achieve cost savings, especially during times of high enterovirus prevalence. Additional study is needed to identify subgroups that may achieve greater cost savings from testing to additionally enhance the efficiency of testing.
Human *Parechovirus* (HPeV)

- Newly described species within *Picronaviridae*.
- Echovirus 22 = HpeV1, Echovirus 23 = HPev2; currently HPeV1-16 genotypes identified.
- HPeV 1 and 2 associated with respiratory and GI symptoms.
- During EV surveillance 1970-2005: HPeV1 accounted for nearly 2% cases, mainly respiratory. Severe disease with 11% mortality.
- Parechovirus 3 was first isolated from stool in a 1 year old child with acute flaccid paralysis in Japan and reported in 2004.

### Table 2. Human parechovirus (HPeV) and enterovirus (EV) prevalence in CSF.

<table>
<thead>
<tr>
<th>Virus</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPeV</td>
<td>16/196 (8.2)</td>
<td>1/239 (0.4)</td>
<td>16/281 (5.7)</td>
<td>33/716 (4.6)</td>
</tr>
<tr>
<td>EV</td>
<td>31/216 (14.4)</td>
<td>37/262 (14.1)</td>
<td>40/283 (14.1)</td>
<td>108/761 (14.2)</td>
</tr>
</tbody>
</table>

Wolther et al CID 2008
HPeV3-CNS infection

- Infants less than 6 months old. Higher prevalence in the first 60 days of life.

- Clinical presentation; sepsis-like illness. Triad of symptoms- irritability (98%), fever (95%), and non-specific rash (59%).

- Poor outcome in European studies: Encephalitis and white matter injury, hepatitis and thrombocytopenia.

- Summer/Fall prevalence June- Oct prevalence.

- CSF pleocytosis absent in majority of the patients. HPeV Vs EV-positive patients: lower peripheral WBC, ANC, ALC, CSF pleocytosis %, higher Tmax and longer duration of fever.

- Laboratory Diagnosis: Realtime RT-PCR. FilmArray ME panel is the only FDA approved assay.
EV-HPeV CNS infections; Kansas City, USA 2006-2016

# infected

<table>
<thead>
<tr>
<th>Year</th>
<th>EV</th>
<th>HPeV</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>81</td>
<td>4</td>
</tr>
<tr>
<td>2007</td>
<td>86</td>
<td>54</td>
</tr>
<tr>
<td>2008</td>
<td>156</td>
<td>0</td>
</tr>
<tr>
<td>2009</td>
<td>55</td>
<td>66</td>
</tr>
<tr>
<td>2010</td>
<td>141</td>
<td>4</td>
</tr>
<tr>
<td>2011</td>
<td>55</td>
<td>4</td>
</tr>
<tr>
<td>2012</td>
<td>42</td>
<td>47</td>
</tr>
<tr>
<td>2013</td>
<td>53</td>
<td>8</td>
</tr>
<tr>
<td>2014</td>
<td>65</td>
<td>43</td>
</tr>
<tr>
<td>2015</td>
<td>181</td>
<td>11</td>
</tr>
<tr>
<td>2016</td>
<td>40</td>
<td>21</td>
</tr>
</tbody>
</table>

EV n= 955, HPeV n= 263

- HPeV3: 44%
- CVA9: 6%
- CVA16: 2%
- CVA2: 0%
- CVA6: 1%
- CVB1: 2%
- CVB2: 2%
- CVB3: 5%
- CVB4: 5%
- CVB5: 3%
- E11: 4%
- E13: 0%
- E18: 13%
- E21: 1%
- E25: 1%
- E27: 3%
- E3: 1%
- E30: 1%
- E4: 1%
- E6: 1%
- E7: 2%
- E9: 2%
- E10: 0%
Table 2: Impact of EV/Par-A RT-PCR Test Result on Antimicrobial Management

<table>
<thead>
<tr>
<th></th>
<th>Par-A (#) (%)</th>
<th>EV pos (#) (%)</th>
<th>Neg (#) (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Test Narrow Spectrum</td>
<td>50 36.5</td>
<td>111 36.51</td>
<td>458 34.7</td>
<td>0.788</td>
</tr>
<tr>
<td>Post-Test Narrow Spectrum</td>
<td>21 15.33</td>
<td>38 12.5</td>
<td>225 17.05</td>
<td>0.146</td>
</tr>
<tr>
<td>Pre-Test Broad Spectrum</td>
<td>105 76.64</td>
<td>224 73.68</td>
<td>904 68.48</td>
<td>0.043</td>
</tr>
<tr>
<td>Post-Test Broad Spectrum</td>
<td>32 23.36</td>
<td>60 19.74</td>
<td>423 32.05</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pre-Test Acyclovir</td>
<td>36 26.28</td>
<td>49 16.12</td>
<td>211 15.98</td>
<td>0.009</td>
</tr>
<tr>
<td>Post-Test Acyclovir</td>
<td>9  6.57</td>
<td>11  3.62</td>
<td>92  6.97</td>
<td>0.097</td>
</tr>
<tr>
<td>Pre-Test Empiric</td>
<td>106 77.37</td>
<td>226 74.34</td>
<td>912 69.09</td>
<td>0.038</td>
</tr>
<tr>
<td>Post-Test Discontinued Empiric</td>
<td>73 68.87</td>
<td>165 73.01</td>
<td>492 53.95</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Table 3: Impact of EV/Par-A RT-PCR Test Result on Discharge Decisions

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Std. Dev</th>
<th>Delta</th>
<th>p-value vs Neg</th>
<th>CI lower</th>
<th>CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of Stay (hours)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Par-A</td>
<td>62.76</td>
<td>40.64</td>
<td>-5.7</td>
<td>0.161</td>
<td>-13.6</td>
<td>2.3</td>
</tr>
<tr>
<td>EV</td>
<td>47.48</td>
<td>27.03</td>
<td>-20.9</td>
<td>&lt;.001</td>
<td>-26.0</td>
<td>-15.8</td>
</tr>
<tr>
<td>Neg</td>
<td>68.42</td>
<td>75.89</td>
<td>-ref</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Time From Results to Discharge (hours)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Par-A</td>
<td>32.77</td>
<td>38.26</td>
<td>-7.7</td>
<td>0.041</td>
<td>-15.2</td>
<td>-0.3</td>
</tr>
<tr>
<td>EV</td>
<td>21.96</td>
<td>30.68</td>
<td>-18.6</td>
<td>&lt;.001</td>
<td>-23.7</td>
<td>-13.5</td>
</tr>
<tr>
<td>Neg</td>
<td>40.52</td>
<td>69.71</td>
<td>-ref</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
FilmArray® Meningitis/Encephalitis Panel

1 Test. 14 Targets. All in about an hour.

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

**Viruses**
- Cytomegalovirus (CMV)
- Enterovirus
- Herpes simplex virus 1 (HSV-1)
- Herpes simplex virus 2 (HSV-2)
- Human herpesvirus 6 (HHV-6)
- Human parechovirus
- Varicella zoster virus (VZV)

**Fungi**
- *Cryptococcus neoformans/gattii*
Multiplex Assay for CSF- Considerations

- Performance- Analytical and Clinical
- Cost
- Patient selection
  - False positive
  - Overutilization
- Test familiarity and Interpretation
- Collaboration with ASP
Multicenter Evaluation of BioFire FilmArray Meningitis/Encephalitis Panel for Detection of Bacteria, Viruses, and Yeast in Cerebrospinal Fluid Specimens

Amy L. Leber, a Kathy Everhart, a Joan-Miquel Balada-Llasat, b Jillian Cullison, b Judy Daly, c Sarah Holt, c Paul Lephart, d Hossein Salimnia, d Paul C. Schreckenberger, a Sharon DesJarlais, a Sharon L. Reed, f Kimberle C. Chapin, g Lindsay LeBlanc, g J. Kristie Johnson, h Nicole L. Soliven, h Karen C. Carroll, i Jo-Anne Miller, i Jennifer Dien Bard, k Javier Mestas, k Matthew Bankowski, l Tori Enomoto, l Andrew C. Hemmert, n Kevin M. Bourzac n

TABLE 1 Positivity rate for the FilmArray ME Panel for all samples and by age group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Positivity</th>
<th>No. of samples</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All samples (n = 1,560)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative samples</td>
<td></td>
<td>1,424</td>
<td>91.3</td>
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<td>Single detections</td>
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<td>Codetections</td>
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<tr>
<td>Age group (n)</td>
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<tr>
<td>&lt;2 mo (299)</td>
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<td>58</td>
<td>19.4</td>
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<tr>
<td>2–23 mo (143)</td>
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<td>17</td>
<td>11.9</td>
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<tr>
<td>2–17 yr (197)</td>
<td></td>
<td>15</td>
<td>7.6</td>
</tr>
<tr>
<td>18–34 yr (224)</td>
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<td>15</td>
<td>6.7</td>
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<tr>
<td>35–64 yr (522)</td>
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<td>23</td>
<td>4.4</td>
</tr>
<tr>
<td>≥65 yr (175)</td>
<td></td>
<td>8</td>
<td>4.6</td>
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</table>

Sensitivity 100% for 9/14 analytes
Specificity 99.2%
FIG 1 Relative performance of the FilmArray ME Panel versus comparator assays after additional discrepancy investigation. Additional discrepancy investigation included other laboratory testing and clinical data (see Table S2 in the supplemental material). FA, FilmArray ME Panel result; FP, false positive, FN, false negative.
Table 1  Summary of standard diagnostic testing performed in patients with community acquired meningitis with pathogens identified by FA ME (n=15)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cerebrospinal (CSF) Fluid</th>
<th>Blood</th>
<th>Sputum</th>
<th>Urine</th>
<th>Stool</th>
<th>FA ME</th>
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<tbody>
<tr>
<td></td>
<td>PCR</td>
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<td>Fungai</td>
<td>AF8</td>
<td>PCR</td>
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<td>Enterovirus</td>
<td>NSV</td>
<td></td>
<td>HIV</td>
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<tr>
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<td>C. neoforans</td>
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<td></td>
<td>NSV</td>
<td></td>
<td>HIV</td>
<td></td>
</tr>
</tbody>
</table>

Blue filled cells Test sent and negative, yellow filled cells Test sent and positive, empty cells Test not sent

HSV Herpes Simplex Virus, EBV Epstein Barr Virus, RPR rapid plasma reagin, HIV Human Immunodeficiency Virus, VZV Varicella Zoster Virus, RAT - , VDRL Venereal Disease Research Laboratory, PCR polymerase chain reaction, AFB Acid Fast Bacillus

* Pathogens not identified by standard evaluation (n = 11 patients)
Mini-Review

Implementation of Rapid Molecular Infectious Disease Diagnostics:
The Role of Diagnostic and Antimicrobial Stewardship

Kevin Messacar MD¹,², Sarah K Parker MD², James K Todd MD MPH², Samuel R Dominguez MD PhD³

Clinical evaluation

Patient

Diagnosis & treatment

Diagnostic Stewardship
- Right test
- Right patient
- Right time

Rapid diagnostic test ordered

Health Care Provider

Antimicrobial Stewardship
- Right interpretation
- Right antimicrobial
- Right time

Rapid diagnostic test performed

Microbiology laboratory

Rapid diagnostic result reported

JCM Accepted Manuscript Posted Online 28 December 2016
Molecular assays for CSF: Advantage

• Tailor the antimicrobial therapy initiation - bacterial versus viral
• Addition of adjunctive therapy - Dexamethasone for *H. influenza* and *S. pneumoniae*
• Optimize exposure to antimicrobial therapy - HSV
• Reduce additional investigations - laboratory, radiological
• Reduce Length of Stay - EV/ParA, HSV
• Improve survival
• Reduce overall healthcare costs
Conclusions

• Meningitis and Encephalitis are potentially life threatening syndromes with myriad of infectious and non-infectious causes
• Rapid etiological diagnosis can improve outcomes. Viral agents (EV/ParA; HSV) and Bacterial agents are leading causes
• Evaluation of current laboratory practices and replace with newer methods
• Identify patient population and clinical findings that will benefit from Multiplex ME panel versus singleplex PCR assays
• Integrate diagnostic stewardship with antimicrobial stewardship program to ensure best patient outcomes