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Potential Clinical Impact of The Filmarray Meningitis Encephalitis Panel In Children With Suspected Central Nervous System Infections

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Abstract

The FilmArray Meningitis Encephalitis Panel, a multiplex PCR for testing of cerebrospinal fluid, was compared to conventional diagnostic methods in children with suspected central nervous system infections. The panel had comparable diagnostic yield (96% agreement) and improved time-to-diagnosis by 10.3 hours with potential for more judicious antimicrobial use, particularly acyclovir.

Keywords

meningitis; encephalitis; central nervous system infection; cerebrospinal fluid; rapid diagnostics; acyclovir

Central nervous system (CNS) infections, including meningitis and encephalitis, lead to significant long-term morbidity, mortality, and high health care costs in children¹⁻⁴. Rapid and accurate detection of pathogens in the cerebrospinal fluid (CSF) can improve clinical care of such children with suspected CNS infections^{5,6}. However, the conventional approach of culture and pathogen-specific polymerase chain reaction (PCR) testing of CSF guided by clinical suspicion is hampered by slow turnaround time and low diagnostic yield resulting in delayed administration of effective therapies and unnecessary empiric administration of broad spectrum antimicrobials⁷⁻⁹.

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The FilmArray Meningitis and Encephalitis Panel (MEP, BioFire Diagnostics/Biomérieux, Salt Lake City, UT) became available in October 2015 for rapid, simultaneous, PCR-based detection in CSF of 14 targets (6 bacteria, 7 viruses, and a yeast) capable of causing CNS infections (Supplemental Table 1)¹⁰. Yet the real-world performance of MEP compared to conventional diagnostic methods remains unknown, as is its potential clinical impact in common clinical scenarios in pediatrics, such as in infants undergoing meningitis evaluation and children with aseptic meningitis and encephalitis. Here we retrospectively compare the diagnostic yield, time-to-diagnosis, and potential clinical impact of MEP to conventional CSF testing ordered by practitioners in children with suspected or confirmed CNS infection.

CSF specimens banked at -70°C by the Microbiology Laboratory at Children's Hospital Colorado, a tertiary care children's hospital in Aurora, CO, were selected from three distinct groups of children enrolled in studies approved by the Colorado Multiple Institutional Review Board. The infant group (INF) included children less than 3 months with CSF tested for enterovirus (EV) or herpes simplex virus (HSV) from January 2010-December 2012. The aseptic meningitis and encephalitis group (AM/E) included children greater than 3 months with fever and CSF pleocytosis (>5 white blood cells $\times 10^3/\mu\text{L}$) with negative CSF bacterial cultures from January 2012-December 2014. The confirmed CNS infection group (POS) included children of any age with a pathogen detectable by MEP and identified in CSF by conventional testing from January-December 2015.

Aliquots of each CSF were tested by MEP and then compared with results of previously-ordered CSF testing ("clinical testing"). Clinical bacterial testing was performed by culture of CSF on solid agar plates and in broth bottles onto a BACTEC system (Becton Dickinson, Sparks MD), with isolate identification by biochemical methods and/or mass spectroscopy. Testing for EV was performed daily "on demand" by Xpert EV RT-PCR (Cepheid, Sunnyvale, CA). HSV was detected by Multicode-RTx HSV RT-PCR (Luminex Corporation, Austin, TX) performed once daily. Discrepant PCR results were resolved by repeating the originally-ordered method on an additional CSF aliquot. Samples with multiple pathogens detected by MEP were retested, as directed by the manufacturer. Clinical testing results, time-to-diagnosis (defined as time from receipt of CSF by the laboratory to time of reporting the organism identification), and acyclovir days (defined as calendar days of acyclovir administered) were collected through chart review. Time-to-diagnosis for MEP was estimated at 3 hours based on an average 2 hour accessioning, sample transport, and reporting time in the Microbiology Laboratory at CHCO with an additional 1 hour for MEP run-time. Time-to-diagnosis for positive samples using clinical testing was compared to the expected value for MEP using a one-sample student t-test with $\alpha=0.05$.

A total of 138 CSF samples were tested (45 INF, 65 AM/E, 28 POS). Overall, 45 (33%) samples were positive by clinical testing and 43 (31%) were positive by MEP, with an overall agreement of 96% (Table 1). Six samples had discrepant results (Table 2): 4 with EV identified by clinical testing were falsely-negative by MEP; 2 samples positive for EV or HSV by MEP were negative by clinical testing. Two samples with multiple pathogens initially detected by MEP (EV+*Streptococcus agalactiae*; EV+HSV) had only EV upon MEP retesting, in agreement with the initial clinical results. A mean 13.3 hour time-to-diagnosis (95% confidence interval: 10.7-16 hours) for pathogens detected by conventional

clinical methods was significantly longer than the expected 3 hours with MEP ($p<0.001$). Acyclovir was administered in 48.9% of INF and 49.2% of AM/E HSV-negative children for a median of 2 and 3 days, respectively.

Our study suggests that MEP can have comparable diagnostic yield and more rapid time-to-diagnosis than conventional clinical testing in children with suspected CNS infection and implies that MEP has considerable potential to improve clinical outcomes through earlier optimization of antimicrobial regimens. For example, rapid detection of EV can decrease unnecessary use of antimicrobials, shorten length of stay and decrease healthcare costs¹¹⁻¹³. The ability of MEP to detect EV, however, may be somewhat less than by our singleplex assay. More rapid HSV detection by MEP has the potential to minimize the unnecessary empiric use of acyclovir in low-risk infants and children, which has doubled over the past decade⁹.

The retrospective nature of our study has inherent strengths and limitations. Our banked CSF samples came from well-characterized cases allowing a realistic comparison of diagnostic yield, turnaround time, and potential clinical impact in specific clinical scenarios frequently encountered in pediatrics. However, the criteria used for sample selection, including exclusion of positive bacterial cultures in the AM/E group and bias towards HSV or EV based on clinically ordered testing in the INF group, likely led to a lower than expected prevalence of pathogens in these groups. In contrast, other studies with less restrictive inclusion criteria have demonstrated the potential for MEP to detect bacterial pathogens that did not grow on culture from children with prior antibiotic exposure and viral etiologies unsuspected by clinicians^{14,15}. Although the potential for MEP detection of persistent, reactivated, or chromosomally integrated herpesviruses, such as human herpesvirus-6, that may not be causing active infection, exists, we did not observe this in our study^{16,17}.

This study demonstrates the potential for significant clinical impact of MEP in pediatric populations commonly evaluated for CNS infection, including rapid diagnosis to enable timely optimization of antimicrobial therapy and reduce unnecessary acyclovir use. Further studies are needed to prospectively evaluate the impact and cost-effectiveness of MEP in the real clinical environment. Effective implementation and antimicrobial stewardship intervention strategies are needed to optimize the impact of MEP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CSF Cerebrospinal fluid

CNS	central nervous system
MEP	FilmArray Meningitis Encephalitis Panel
PCR	polymerase chain reaction

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- The FilmArray MEP had 96% agreement with conventional diagnostic methods.
- Time-to-diagnosis with MEP was 10.3 hours faster.
- MEP creates potential for more judicious acyclovir use in children.

Pathogens Identified in the Cerebrospinal Fluid of Children with Suspected Central Nervous System Infection by FilmArray Meningitis Encephalitis Panel Compared to Conventional Clinical Diagnostic Testing

Table 1

Pathogens Detected	Infants (n=45)		Aseptic Meningitis/Encephalitis (n=65)		ME Panel Pathogen Previously Identified in CSF (n=28)		TOTAL (n=138)	
	Clinical Testing	ME Panel	Clinical Testing	ME Panel	Clinical Testing	ME Panel	Clinical Testing	Percent Agreement
Enterovirus	6 (13%)	5 (11%)	10 (15%)	9 (14%)	20 (71%)	19 (68%)	36 (26%)	96%
Herpes simplex virus	0 (0%)	0 (0%)	1 (2%)	2 (3%)	3 (11%)	3 (11%)	4 (3%)	99%
<i>Streptococcus agalactiae</i>	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (11%)	3 (11%)	3 (2%)	100%
<i>Escherichia coli</i>	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	1 (4%)	1 (1%)	100%
<i>Haemophilus influenzae</i>	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	1 (4%)	1 (1%)	100%
ALL PATHOGENS	6 (13%)	5 (11%)	11 (17%)	11 (17%)	28 (100%)	27 (96%)	45 (33%)	96%

Table 2
Summary of Discrepant Results Between FilmArray Meningitis Encephalitis Multiplex PCR Panel Compared to Clinical Testing of Cerebrospinal Fluid Samples from Children with Suspected Central Nervous System Infection

Clinical Testing Result (Method)	FilmArray Meningitis Encephalitis Panel	Follow-up Test: Result	Conclusion (Clinical Scenario)
1 EV (Xpert EV)	Negative	Xpert EV #2: positive MEP #2: positive	False negative MEP#1 (EV meningitis)
2 EV (Xpert EV)	Negative	Xpert EV #2: positive MEP #2: negative	False negative MEP#1 +2 (EV meningitis)
3 EV (Xpert EV)	Negative	Xpert EV #2: positive MEP #2: insufficient sample	False negative MEP#1 (EV meningitis)
4 EV (Xpert EV)	Negative	Xpert EV #2: positive MEP #2: positive	False negative MEP#1 (EV meningitis)
5 Negative (Xpert EV)	EV	Xpert EV #2: positive MEP #2: positive	False negative clinical testing by Xpert EV (EV-A71 meningitis; virus identified in stool)
6 Negative (Multicode-RTx HSV RT-PCR)	HSV	HSV RT-PCR (Mayo): negative	False negative clinical testing by HSV RT-PCR (meningitis in teen with HSV culture negative skin vesicles clinically treated with acyclovir despite negative HSV CSF PCR)