BRIEF REPORT

Cerebrospinal Fluid Analysis With the BioFire FilmArray Meningitis/Encephalitis Molecular Panel Reduces Length of Hospital Stay in Patients With Suspected Central Nervous System Infections

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The Meningitis/Encephalitis Panel (MEP) is a sensitive and specific Food and Drug Administration–approved molecular diagnostic test for the 14 most common infectious etiologies of meningoencephalitis. Using a before–after controlled study design, MEP reduced length of hospital stay by 1.5 days, and this effect was mediated by the reduced time to final microbiology reporting.

Keywords. bacteria; length of stay; molecular diagnostics; meningoencephalitis; virus.

Meningitis and encephalitis are infrequent but potentially fatal central nervous system infections (CNSIs). These CNSIs are difficult to diagnose clinically and require cerebrospinal fluid (CSF) analyses to support their diagnosis and identify a potential pathogen [1]. In patients suspected of having meningitis who present with the classic clinical triad of fever, headache, and normal mental status, only 25%–30% will demonstrate CSF pleocytosis, and only 1%–2% will have a positive CSF culture [2, 3]. The clinical exam is even less helpful for patients suspected of having encephalitis, with the majority of positive CSF cultures identifying enteroviral infections that are not amenable to antiviral therapy [2, 3]. This means that patients with suspected CNSIs are admitted to hospital and receive empiric antimicrobial therapy while waiting for their final CSF microbiologic results to be reported, almost all of which are negative

or therapeutically irrelevant [2]. Using our current microbiologic technologies, this means that most patients with suspected CNSIs are hospitalized for ≥48 hours.

The BioFire FilmArray MEP is a molecular diagnostic test that uses a proprietary multiplex polymerase chain reaction (PCR) system to rapidly, within 1 hour, identify 14 different viral, bacterial, and fungal pathogens in cerebrospinal fluid [4]. The MEP has been Food and Drug Administration–approved for use in community-acquired CNSIs [4]. The MEP test characteristics have been reported; the negative and positive predictive values are 99.9% and 95.2%, respectively, compared with culture-based standards [4]. The laboratory costs of using the MEP include the cost of the proprietary PCR system ($50 000 CDN), along with the service contract ($4000/year CDN) and the cost per test ($200 CDN) (personal communication, Nellie Bradbury). Two previous studies examined the cost-effectiveness of using MEP compared with standard of care (SOC) [5, 6]. One study developed an economic model for potential savings on overall costs of care [5], whereas the other was a real-world analysis of overall costs of antimicrobials [6]. The impact of MEP on overall hospital costs was significant, but savings from antimicrobials alone were negligible. There has been no real-world study to determine the impact of MEP on length of hospital stay, which would be the greatest driver of costs for CNSI cases.

We conducted a single-center, controlled before (B)–after (A) study to estimate the impact of the MEP on time to hospital discharge (TTD) in suspected CNSI cases and the potential cost savings associated with this reduced length of stay. The study was conducted at the Royal Victoria Regional Health Centre, a 399-bed, community-based, university-affiliated hospital in central Ontario, Canada. The TTDs of consecutive patients admitted with suspected CNSI between April 1, 2016, to March 31, 2017, who received SOC CSF analyses (B period) were compared with similar patients admitted between April 1, 2017, and March 31, 2018, who had their CSF tested using the MEP (A period). The SOC CSF analyses in the control period were physician-dependent and could have included any of the following: cell count, glucose, protein, bacterial stain and culture, herpes simplex virus PCR (send-out test), enterovirus PCR (send-out test), and/or fungal stain and culture. Differences in the TTD (Δ TTD) were estimated using treatment effects regression analysis. The advantage of treatment effects regression over Cox proportional hazards regression is that the data can still be modeled as time to event without the need for the assumption of proportional or constant hazard rates. We used both inverse probability weighting and regression adjustment to ensure a doubly robust estimate for Δ TTD. Differences in TTD were

estimated for the entire sample and for a subset of the sample that was administratively censored at 18 days (upper limit of 95% confidence interval for length of stay). Age, sex, and final CSF result (positive, negative, or not done) were included in the inverse probability weighting portion of the model, whereas age and sex were included in the regression adjustment portion of model. Differences in time to final microbiology reporting (TTMR) and time to definitive antimicrobial therapy (TTDAT) were considered possible mediators for any differences in the primary outcome by forcing them into the baseline regression model. Mediators, partial or complete, will result in a decreased Δ TTD when added to the baseline regression model. The size of the reduction in Δ TTD caused by TTDAT and/or TTMR will indicate how important each factor is, if at all, in mediating Δ TTD. TTMR was defined as the absolute difference in time (hours) between the documented receipt of the CSF sample in the microbiology laboratory and the documented time of final reporting by the microbiology technician. TTDAT was defined as the absolute difference in time (hours) between the documented time of administration between the first empiric dose of antimicrobial and the documented time of the first administration of a pathogen-specific antimicrobial or discontinuation of the last administered dose of empiric antimicrobial. *T* test statistics were used to compare all continuous variables, and chi-square test statistics were used to compare all categorical variables. *P* values ≤.05 were considered significant.

Potential cost savings were estimated using the Ministry of Health and Long-Term Care's Case Costing Analysis Tool [7]. For 2015/2016, the most recent year for which we have data, the overall costs of hospitalization for CNSI cases (SD) were $12 264 CDN ($25 410 CDN), with a mean length of hospital stay (SD) of 8.5 (11.4) days. These costs and length of stay were based on 747 CNSI cases. So, using the SD to estimate the standard error (SE), the 95% confidence intervals for cost and length of stay are $10 442 to $14 086 and 7.7 to 9.3, respectively. On average, each day in the hospital costs ~$1442 CDN (95% confidence interval [CI], $1356 to $1514 CDN). As the mean microbiology costs during this same period (SD) were $364 CDN ($754 CDN), any extra costs attributable to the MEP were likely offset by the SOC diagnostic costs and so were not included in the final cost savings estimates. The potential cost savings were estimated by simply multiplying the Δ TTD by $1442 per day to get an approximate estimate.

The total sample size was 117 patients (64 [B] vs 53 [A]) (Table 1). The patients were matched for age, sex, intensive care unit admissions, and deaths. Both groups had similar numbers of CSF analyses completed (89% [B] vs 85% [A]; NS). The numbers of positive CSF analyses were similar (22% [B] vs 22.6% [A]; NS). The majority of positive CSF analyses were viral (86% [B] vs 91.6% [A]; NS). In group B, 66.7% of the viral infections were due to herpes viruses, compared with 45.4% in group A (NS). The total hours of antimicrobial therapy did not differ between the 2 groups. There was also no difference

Table 1. Patient Demographics and CSF Results

Variable	Pre-CSF Panel (n = 64)	Post-CSF Panel (n = 53)	Test Statistic[a] (*P* Value)
Sex, No.			.56 (.45)
Female	33	31	
Male	31	22	
Age (SD), y	51.3 (20.7)	43.99 (25.7)	1.67 (.098)
ICU admission, No. (%)	12 (18.7)	5 (9.4)	2.03 (.15)
Deaths, No. (%)	3 (4.7)	7 (13.2)	2.69 (.10)
CSF exams completed, No. (%)	57 (89)	45 (84.9)	.45 (.50)
CSF results, No.			.51 (.77)
Negative	43	33	
Positive	14	12	
Not done	7	8	
CSF microbiology, No.			.96 (.81)
Negative	43	33	
Viral	12	11	
Bacterial	1	1	
Fungal	1	0	
CSF microbiology species, No.			5.23 (.81)
Varicella-zoster	4	3	
Enterovirus	3	5	
HSV-2	3	2	
HSV-1	1	0	
JC	1	0	
West Nile	0	1	
Neisseria meningitidis	1	1	
Cryptococcus neoformans	1	0	

Abbreviations: CSF, cerebrospinal fluid; HSV, herpes simplex virus; ICU, intensive care unit; JC, john Cunningham virus.

[a]Chi-square test statistic for all categorical variables and *t* test statistic for all continuous variables.

between the reasons for changes to empiric therapy, with the majority being due to discontinuation of some or all of the empiric regimen (80% [B] vs 94% [A]; NS). The overall Δ TTD differed between the 2 groups and was approximately 1.5 days after accounting for age and sex (Table 2). Forcing time to definitive antimicrobial therapy (TTDAT) into the model did not change the Δ TTD, suggesting that this was not a mediator of the reduced length of stay in patients whose CSF was analyzed using MEP. However, forcing time to final microbiology reporting (TTMR) into the model resulted in failure of convergence, suggesting that the average treatment effect on time to discharge was accounted for by the TTMR (Table 1). A separate analysis for TTMR demonstrates a point estimate for Δ TTMR that is nearly identical to the Δ TTD, supporting the conclusion that the reduction in length of stay in the MEP-exposed group compared with the SOC group is almost all due to earlier reporting of the final CSF results (Table 1).

The potential cost savings per case associated with using the MEP were estimated to be $2319 CDN (95% CI for point estimate of Δ TTT = −38.6 hours, −83.6, 6.5). The 95% CI for potential cost savings using the range of Δ TTD and cost of $1442 per day of hospitalization was −$390 to $5022 CDN.

Table 2. Differences in Primary and Secondary Outcomes

Outcome	Effect Size, h	95% Confidence Interval
n = 117		
Mean length of stay (B period)	494.7	275.1 to 714.4
Average treatment effect (Δ TTD)	−250.4	−491.9 to −8.8
n = 95 (only includes patients with TTD ≤18 d)		
Mean length of stay (B period)	149.6	121.7 to 177.5
Average treatment effect (Δ TTD + age + sex)	−38.6	−83.6 to 6.5
(Δ TTD + age + sex + TTDAT)	−37.2	−82.0 to 7.6
(Δ TTD + age + sex + TTMR)		Model doesn't converge
n = 117		
Mean time to final microbiology reporting	56.4	32.7 to 80.2
(Δ TTMR)	−28.7	−55.1 to −2.4
n = 95 (only includes patients with TTD ≤18 d)		
Mean time to final microbiology reporting	62.9	34.1 to 91.8
(Δ TTMR)	−33.8	−67.1 to −0.5

Abbreviations: TTD, time to hospital discharge; TTMR, time to final microbiology reporting.

We were able to demonstrate that the use of the MEP in patients admitted with suspected CNSI is associated with a reduced length of stay of approximately 1.5 days. Almost all of this effect is attributable to a faster turnaround time to reporting of microbiology results. In centers like ours, in which some CSF microbiology tests must be sent out to specific testing laboratories, the MEP affords our patients and their health care providers the opportunity to minimize exposure to unnecessary antimicrobials and prolonged hospital admissions due to faster reporting. It is worth noting that our reduced length of stay in the MEP group was not a result of patients being discharged directly from the emergency department (12.5% [B] vs 18.8% [A]; NS). Our estimated cost savings were consistent with those reported in a previous study that predicted savings of $2157 (UDS) per CNSI case that demonstrated CSF pleocytosis [5]. Given the ease of sample processing associated with the MEP system, centers with minimal expertise could easily implement this system in their microbiology laboratories with the reasonable expectation of a positive return on investment when the MEP is used on admitted patients with CSF pleocytosis [8].

References

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