Diagnostic Microbiology and Infectious Disease 93 (2019) 349–354

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Cost of managing meningitis and encephalitis among infants and children in the United States☆

Joan M Balada-Llasat [a,*], Ning Rosenthal [b], Rodrigo Hasbun [c], Louise Zimmer [d], Samuel Bozzette [b,e], Steven Duff [f], Jessica Chung [b], Christine C. Ginocchio [d,g]

[a] Department of Pathology, The Ohio State University Wexner Medical Center, OH
[b] Premier Applied Sciences, Premier Healthcare Solutions Inc., Charlotte, NC
[c] University of Texas Health Science Center, Houston, TX
[d] bioMérieux, Durham, NC
[e] University of California, San Diego, CA
[f] Veritas Health Economics Consulting, Carlsbad, CA
[g] Hofstra Northwell School of Medicine, Hempstead, NY

ARTICLE INFO

Article history:
Received 11 May 2018
Received in revised form 15 October 2018
Accepted 16 October 2018
Available online 27 October 2018

Keywords:
Meningitis
Encephalitis
Cost
Diagnosis
Infants
Children

ABSTRACT

A retrospective cohort study design was used to assess the use and costs of diagnostic tests, medication, and total hospitalization costs for pediatric patients with suspected meningitis/encephalitis who received a lumbar puncture (LP) procedure. Related costs were calculated by timing of LP performed and infectious etiology for infants (<1 year) and children (1–17 years). A total of 3030 infants and 3635 children with suspected ME diagnosed between 2011 and 2014 were included in the study. The mean hospitalization cost for infants and children was $12,759 and $11,119, respectively, with medication and laboratory test costs of $834 and $1771 for infants and $825 and $855 for children, respectively. Total visit cost increased with delayed LP procedure, ICU stay, and if the etiology was viral (other than enterovirus or arbovirus) or bacterial. Higher diagnostic and treatment costs were associated with delayed LP procedure, etiologic agent, and ICU stay.

1. Introduction

Meningitis and encephalitis (ME) are often caused by pathogens such as bacteria, viruses, fungi, and parasites (Castelblanco et al., 2014; Richie and Josephson, 2015). Vaccination for *Haemophilus influenzae* type b, pneumococcal, and meningococcal vaccines in the United States (US) and the use of maternal prophylaxis for group B *Streptococcus* have reduced the prevalence of bacterial infections, and now the most common ME pathogens are viruses (Romero and Newland, 2003; Thigpen et al., 2011). Of the 72,000 hospitalizations reported in the US due to meningitis in 2006, more than half were caused by viruses (Holmquist et al., 2006). Although hospitalizations have continued to decline, the clinical and economic burden of ME remains substantial. For example, viral meningitis, a self-limiting condition, may lead to hospital admission and overuse of antibiotics and testing (Castelblanco et al., 2014; Davis et al., 2011; MacNeil et al., 2015; Nigrovic et al., 2013).

Diagnosing ME is challenging because many etiologic agents present with similar signs. There is high risk of morbidity and mortality especially with bacteria and herpes simplex virus (HSV) etiologies; for this reason, many patients are admitted and treated empirically, resulting in higher costs (Nigrovic et al., 2013; Richie and Josephson, 2015; Shukla et al., 2017). If treatment is delayed or inappropriate, severe complications such as severe and irreversible neurological damage may occur, resulting in prolonged hospital stays (Hasbun et al., 2013; Khoury et al., 2012). One of the challenges of laboratory diagnosis is that traditional culture testing may take up to 72 h for bacteria or longer for fungi. Furthermore, certain pathogens will not grow, and results may be negative if the patient received empiric antibiotic treatment. Currently, most of the diagnosis of viruses relies on molecular assays. Owing to the lack of approved molecular assays and laboratory expertise, or cost, many institutions send their specimens to a reference laboratory, which causes a notable delay in diagnosis. In general, the use of rapid

☆ Conflict of interest: SD is a paid consultant to bioMérieux and an employee of Veritas Health Economics Consulting; RH and JMBL are consultants to bioMérieux and speakers for BioFire Diagnostics; CCG is an employee of bioMérieux and BioFire Diagnostics; LZ is an employee of bioMerieux and SB is a former employee of bioMérieux and currently an employee of Premier Research Services. NR is an employee of Premier Applied Sciences. JC was an employee of Premier Applied Sciences when this work was done.

* Corresponding author. Tel.: +1-614-257-2785 (Office).
E-mail address: Joan.balada@osumc.edu (J.M. Balada-Llasat).

https://doi.org/10.1016/j.diagmicrobio.2018.10.012

diagnostic assays offered on site should improve diagnosis and patient outcomes (Leber et al., 2016).

In order to assess the related costs of management of pediatric patients with suspected ME, a retrospective cohort study was conducted to estimate the cost of testing, treatment, and total hospitalization. Cost was reported by timing of lumbar puncture (LP) performed and by type of pathogen causing the infection. We hypothesized that higher diagnostic and treatment costs may be associated with delayed LP procedure, etiologic agent, and if ICU stay is required.

2. Materials and methods

2.1. Data source

Data for this study were extracted from the deidentified Premier Healthcare Database (PHD). The PHD is a complete census of inpatient and hospital-based outpatient visits including emergency room visits from 631 hospitals, including both children's hospitals and adult/pediatric hospitals, across all 50 states and contains approximately 20% of all hospital discharges in the US since 2000. The hospitals in PHD represent hospitals of all sizes, of both urban and rural origin, and of both academic and nonacademic settings. The majority of the patients came from comprehensive hospitals instead of pediatric hospitals. The PHD data are extracted from standard hospital discharge files and include patients' demographics, disease status, medications and devices used, tests performed, and information on date-stamped billed services in patients' daily service records. Over two-thirds of hospitals submit cost data directly from their Chargemaster, and the remaining hospitals submit current copies of their Medicare Hospital Cost Report and Cost to Charge Ratios at the department or revenue center level to calculate patient-level cost. All cost data in PHD are validated by comparing the aggregate cost for the submitted patient data to financial reports generated by each hospital for the associated time period with less than 2% of difference being considered valid. Patients can be tracked across visits within facilities with a unique identifier. About 25% of participating hospitals voluntarily contribute microbiology data to the PHD. The PHD data are HIPAA compliant according to 45 CRF 46.101(b)(4) and 45 CRF 164.506(d)(2)(ii)(B).

2.2. Study population

The study population included pediatric patients: infants (<1 year) and children (1–17 years) with principal or secondary International Classification of Diseases (ICD)-9 discharge diagnosis codes for ME and who received an LP procedure (ICD-9 procedure code of 03.31 or a Current Procedural Terminology code of 62,270) during an emergency department (ED) visit or during the first 2 service days of an inpatient stay between 2011 and 2014.

All LP procedures performed during the index hospital visit were included in the LP-related cost estimate, except for patients with cryptococcal meningitis. Cost information was submitted by the hospitals, with the majority of cost estimates coming from the charge master. For cryptococcal meningitis patients with multiple LPs performed during the same hospitalization, only the first LP procedure was included in the LP-related cost estimate. Patients admitted with any type of trauma as determined by the hospital, chronic meningitis (ICD-9 diagnosis code: 322.2), CSF shunt, craniotomies, spinal procedures, or head trauma with CSF leaks during the 30 days prior to admission and at time of admission were excluded (ICD-9 diagnosis codes: V45.2, 01.xx, 02.xx, 03.xx, 04.xx, 05.xx, 81.0x, 81.3x, 81.6x, 349.89, 388.61).

2.3. Outcomes

Treatment, diagnosis-related costs, and cost by pathogen type were the primary outcomes studied. Furthermore, the number of the most commonly performed tests from CSF specimens and cost were calculated by capturing the comparable test orders. Due to major differences in coding of the tests, not all were able to be included, especially if those tests were performed in different facilities. These included Gram stain, glucose, protein, cell count and differential, culture (bacterial, acid fast bacteria [AFB], fungal, viral), serum antibody tests (West Nile virus [WNV], Lyme disease, *Coccidioides spp*., HSV, *Cryptococcus spp*., cytomegalovirus [CMV], varicella zoster virus [VZV]), PCR (HSV, EV, Lyme disease, WNV, *Mycobacterium tuberculosis*, Epstein Barr virus [EBV], human herpesvirus 6 (HHV-6), Cryptococcal antigen test, India Ink stain, and ME-diagnosis–related antigen tests.

2.4. Statistical methods

Descriptive data were summarized using frequencies and percentages for categorical variables and using mean (standard deviation) or median (interquartile range) for continuous variables for each subgroup. The χ^2 or Fisher exact test was used to compare the differences between subgroups for categorical variables. The 2-sample independent *t* test was used for comparing differences in continuous variables. Cost was adjusted to 2015 US dollars based on the Consumer Price Index for all urban consumers for hospital and related services. All analyses were performed using SAS (v9.4) (SAS Institute Inc. Cary, NC).

3. Results

A total of 6665 pediatric patients were included in the study sample. Of these, 3030 were infants and 3635 children. Slightly over half (55.3% infants and 59.8% children) were female. About two-thirds of infants and half of the children had private insurance, and 33.2% of infants and 43.9% of the children had public insurance; only 3–3.7% were uninsured. Overall, 91.1% of infants and 76.3% of the children were admitted to hospital.

CSF Gram stain, glucose, protein, and cell count/differential were recorded for infants/children at 84.6–85.2%, 64.9–62.9%, 63.5–64.4%, abd 53–51.5% of patients, respectively (Table 1). CSF acid fast bacilli [AFB] and fungal cultures, antibody tests, cryptococcal antigen test, India Ink, and other antigen tests were conducted for 0.2–6.5% of patients, with higher percentage in children. Overall, PCR tests were only conducted for 12.7% of the infants and 10.2% of the children (Table 1).

Among patients with available microbiology data, approximately 54% (1635 infants and 1947 children) had CSF bacterial culture performed. Of these, 11% and 5% were positive for infants and children, respectively; 266 of the infants and 183 of the children had CSF viral culture, of which 29% and 25% were positive, respectively. Furthermore, 2564 of the infants and 3096 of the children had CSF Gram stain, of which 12% and 6% were positive respectively (Table 1 and data not shown).

The mean cost of laboratory tests ranged from a high of $94 for PCR and bacterial culture to a low of $7 for India ink stain (Table 1). The related cost by patient based on location (outpatient, inpatient ED, or after admission) and timing (first or second day after admission) of LP performed was calculated (Table 2). The mean total visit cost was $12,759 for infants and $11,119 for children, of which mean costs of $2965 for infants and $3097 for children were incurred prior to the LP procedure. The median length of hospital stay was greater in both age groups when the LP was performed on the second service day (infants: median 10 days and children 7 days) as compared to 6 days for infants and 4 days for children who received their LP on the first service day. Higher mean costs were associated with inpatients and with delayed LP $20,226–22,774 (LP first day after admission-procedure done within 24 h after admission) and $24,133–24,624 (inpatient, LP second day after admission, infant/children). Overall, 18.6% of infants and 13.9% of children required an ICU stay with an associated average cost of $23,344 and $30,631 for infants and children, respectively. The percentage of patients with an ICU stay increased from 14.1–15.7% among

Table 1
Number of tests from CSF for which comparable tests orders could be determined.[a]

Variables	Infants (<1 year)			Children (1–17 years)		
	N	%	Cost (2015 US dollars, mean ± STD)	*N*	%	Cost (2015 US dollars,mean ± STD)
Gram stain	2564	84.6	36 ± 26	3096	85.2	33 ± 25
Glucose	1966	64.9	13 ± 12	2287	62.9	13 ± 11
Protein	1924	63.5	16 ± 15	2339	64.4	14 ± 12
Cell count and differential	1607	53	28 ± 22	1873	51.5	41 ± 49
Bacterial culture	1635	54	28 ± 18	1947	53.6	28 ± 20
AFB culture	20	0.7	NA	121	3.3	40 ± 33
Fungal culture	26	0.9	50 ± 35	131	3.6	37 ± 32
Antibody tests[b]	18	0.6	68 ± 48	237	6.5	69 ± 93.
Any PCR test[c]	384	12.7	94 ± 88	372	10.2	88 ± 101
Cryptococcal antigen	5	0.2	40 ± 25	21	0.6	27 ± 15
Viral culture	266	8.8	106 ± 155	183	5	66 ± 60
India ink stain	10	0.3	7 ± 10	38	1.1	10 ± 7
Other antigen tests	11	0.4	11 ± 48	28	0.8	23 ± 24

NA = not available.
[a] Due to major differences in coding of tests, not all were captured.
[b] Among all patients who had antibody tests, 43.75% were tested for WNV, 15.23% for Lyme disease, 11.53% for Coccidioides, 9.89% for HSV, 1.32% for Cryptococcus, 0.88% for CMV, 0.85% for VZV, and 24.55% for other pathogen.
[c] Among all patients who had PCR test, 52.25% were tested for HSV, 44.25% for enterovirus, 8.61% for Lyme disease, 5.56% for WNV, 3.15% for AFB, 1.19% for EBV, 0.35% for HHV, and 2.95% for other pathogen.

inpatients with LP done in the ED to 35.2–33.3% in inpatients with LP done on the second day after admission (Table 2).

The mean medication cost was $834 for infants and $1771 for children. The diagnostic laboratory cost was $825 for infants and $855 for children; of these, the ME-related laboratory test costs were $204 for infants and $172 for children, respectively. Since the majority of laboratories do not perform molecular tests in-house but send out tests, the ME-related laboratory test costs were much lower than expected as the reference laboratory testing cost was not captured in these data. Costs for medication treatment and laboratory testing were lower for outpatients but higher across categories (inpatient with ED LP, inpatients with LP 1 day after admission, and inpatients with LP 2 days after admission) (Table 2).

Enterovirus was the most common etiology in both infants and children, followed by "unknown pathogen" and bacteria. (Table 3) A total of 58.1% of the infants had a diagnosis of ME due to EV (58.1%), 18.4% to bacteria, 1.7% to herpes viruses group (HSV1/2, VZV, CMV, HHV6), and 1.2% to other viruses. In addition, 18.8% had no pathogens identified (Table 3). Among children, 58.6% had a diagnosis of ME due to EV, 8.6% to bacteria, 1.5% to herpes virus group, 1% to arbovirus, and 0.3% to other viruses. A larger percentage of children than infants had no pathogens identified (26.9% vs. 18.8%) (Table 3).

When cost was calculated based on ME etiology, infants diagnosed with unknown etiology had the highest associated hospitalization cost of $41,397, followed by herpes virus ($36,625) and bacterial etiologies ($27,638). For children, herpes virus ME had the highest associated hospitalization cost of $30,906, followed by other viruses ($29,676) and bacterial etiologies ($21,961). The total cost incurred until LP procedure date was highest in the other virus group for infants ($4126) and children (6413), followed by bacterial and herpes virus group for infants, and herpes virus, arbovirus, and bacteria for children. Mean ICU costs were highest for infants diagnosed with herpes virus followed by other virus (60% infants, 58.3% children), unknown pathogens, and bacteria. The highest ICU-related cost was for herpes virus ($46,106) for infants and other virus ($38,485) for children.

For infants, the overall medication cost was highest in the herpes virus group ($2792), followed by other virus ($2647) and bacterial groups ($1768). For children, the overall medication cost was highest in the other virus group ($4727), followed by herpes virus ($4631) and bacterial groups ($2873). The highest ME-related laboratory test cost was for herpes virus ($501 infants and $463 children) followed by other virus ($474 infant and $247 children) (Table 3). The cost was lower as expected because we could not capture the send-out test costs, especially those pathogens detected by molecular methods.

4. Discussion

In this study, we calculated the cost of managing ME among infants and children in the US. We calculated the overall hospitalization and diagnosis-related costs of patients with ME who received an LP procedure in a hospital setting. Our findings show that the cost increased with delayed diagnosis (especially if the LP was delayed), if the patient required an ICU stay, and by infectious agent. Despite advances in the management of infectious ME, diagnosis is challenging because the clinical presentation is nonspecific and many diagnostic tests have low sensitivity. The high potential for morbidity and mortality caused by bacteria and HSV and delayed diagnosis encourages clinicians to treat the majority of patients empirically (Beckham and Tyler, 2006; Whitley and Lakeman, 1995). However, a lumbar puncture is required for more definitive diagnosis, and our data show that delays in LP testing and identification of etiology increase costs associated with other testing and the likelihood of inappropriate treatment. In this study, the majority of ME cases were caused by enterovirus. As other studies have shown, early diagnosis of EV is associated with reduced antibiotic use, decreased length of stay, fewer diagnostic tests (CT and MRI), better outcomes, and lower cost (Ramers et al., 2000).

The use of a rapid test to rule out HSV has been shown to have an impact on the duration of acyclovir therapy (Van et al., 2017). Furthermore, HSV may be missed if the patient does not show the typical CSF presentation, which can lead to additional testing, a longer ICU stay, negative patient impact, and increased costs (Beckham and Tyler, 2006; Tunkel et al., 2008).

Sixty percent of infants with ME caused by "other" viruses (excluding herpes virus, enterovirus, and arbovirus) required an ICU stay followed by those with bacterial (40%) and herpes virus etiologies (32.1%). Similar results were observed for children (other virus 58.3%, bacteria 30.9%, herpes virus 34%); however, 50% of patients with arbovirus also required an ICU stay (Table 3). Unsurprisingly, based on the high cost of ICU care in the US, most of the hospitalization cost is driven by ICU stay (Halpern and Pastores, 2010). Total costs were also affected by medication and laboratory testing costs. The mean overall medication cost for infants was $834 and markedly increased for children (mean cost of $1771). The highest medication costs for both groups were for ME caused by viruses other than enterovirus (Table 3), ranging from $2647–$2792 for infants to $3408–$4727 for children. ME-related laboratory tests accounted for 25% of total laboratory costs for infants and 20% for children. Higher laboratory costs were associated with patients with viral diagnoses. Based on the low ME-related laboratory

Table 2
Related cost by timing of LP performed among the study population.

	Infants (<1 year)					Children (1–17 years)				
	Total	Outpatients with LP in ED[a]	Inpatients with LP in ED[b]	Inpatients with LP 1 day after admission[c]	Inpatients with LP 2 day after admission[d]	Total	Outpatients with LP in ED[e]	Inpatients with LP in ED[f]	Inpatients with LP 1 day after admission[g]	Inpatients with LP 2 day after admission[h]
Unique patients	3030	260	2087	586	88	3635	847	2169	513	93
Total visit cost (mean ± STD)	12,759 ± 19,330	1643 ± 1421	11,612 ± 16,109	20,226 ± 27,757	24,133 ± 26,103	11,119 ± 34,904	1623 ± 1525	11,546 ± 36,027	22,774 ± 51,934	24,624 ± 26,765
Total cost incurred till LP procedure day (mean ± STD)	2965 ± 2266	1362 ± 877	2805 ± 1795	3682 ± 2847	6943 ± 4076	3097 ± 3021	1349 ± 1144	3087 ± 2506	5038 ± 4059	8788 ± 5118
Number of patients with an ICU stay *n* (%)	562 (18.6%)	N/A	328 (15.7%)	203 (34.6%)	31 (35.2%)	504 (13.9%)	N/A	305 (14.1%)	168 (32.8%)	31 (33.3%)
ICU-related cost (mean ± STD)	23,344 ± 26,718	N/A	19,276 ± 23,293	28,650 ± 30,343	31,648 ± 28,161	30,631 ± 76,482	N/A	29,992 ± 86,230	32,457 ± 63,269	27,027 ± 20,272
Medication treatment cost (mean ± STD)	834 ± 1887	71 ± 124	761 ± 1740	1340 ± 2428	1546 ± 2743	1771 ± 9965	127 ± 286	1950 ± 11,869	3363 ± 9418	3982 ± 7986
Diagnostic laboratory testing cost (mean ± STD)	825 ± 1104	348 ± 215	803 ± 957	1059 ± 1513	1240 ± 1906	855 ± 2136	339 ± 674	858 ± 2291	1564 ± 2757	1662 ± 1993
ME-related laboratory tests cost (mean ± STD)	204 ± 234	101 ± 138	218 ± 236	201 ± 251	191 ± 226	172 ± 239	99 ± 113	177 ± 248	247 ± 296	241 ± 270

STD = standard deviation; N/A = not applicable.

[a] Discharge diagnosis: bacteria (26), herpes virus (1), enterovirus (34), other virus (1), unknown pathogens (198). Based on primary and secondary diagnosis coding or transfer to different facility.

[b] Discharge diagnosis: bacteria (346), herpes virus (33), enterovirus (1407), other virus (24), unknown pathogens (229), non-ME diagnosis (48).

[c] Discharge diagnosis: bacteria (148), herpes virus (14), enterovirus (290), other virus (10), unknown pathogens (118), non-ME diagnosis (6).

[d] Discharge diagnosis: bacteria (37), herpes virus (5), enterovirus (25), unknown pathogens (21).

[e] Discharge diagnosis: bacteria (40), herpes virus (2), enterovirus (353), other virus (1), unknown pathogens (444), non-ME diagnosis (7). Based on primary and secondary diagnosis coding or transfer to different facility.

[f] Discharge diagnosis: bacteria (192), herpes virus (29), arbovirus (15), enterovirus (1499), other virus (7), fungi (2), unknown pathogens (333), non-ME diagnosis (92).

[g] Discharge diagnosis: bacteria (70), herpes virus (13), arbovirus (21), enterovirus (238), other virus (3), fungi (1), unknown pathogens (153), non-ME diagnosis (14).

[h] Discharge diagnosis: bacteria (9), herpes virus (6), enterovirus (36), other virus (1), unknown pathogens (39), non-ME diagnosis (2).

Table 3
Costs for the study population with ME by pathogen type.

	Infants (<1 year)						
	Total[a]	Bacteria	Enterovirus	Herpes virus[c]	Arbovirus	Other virus	Unknown pathogens
Number of unique patients (%)	3030	558 (18.4%)	1761 (58.1%)	53 (1.7%)	0	35 (1.2%)	569 (18.8%)
Hospitalization cost (mean ± STD)	12,759 ± 19,330	27,638 ± 26,208	6805 ± 8629	36,625 ± 30,850	N/A	41,397 ± 30,948	13,149 ± 22,226
Cost incurred till LP (mean ± STD)	2965 ± 2266	3840 ± 3137	2737 ± 1811	3517 ± 2551	N/A	4126 ± 2650	2731 ± 2292
Patients with ICU stay *n* (%)	562 (18.6%)	223 (40%)	180 (10.2%)	17 (32.1%)	N/A	21 (60%)	111 (19.5%)
ICU-related cost (mean ± STD)	23,344 ± 26,718	26,255 ± 25,210	13,233 ± 19,809	46,106 ± 39,407	N/A	36,103 ± 29,893	28,726 ± 30,998
Total medication cost (mean ± STD)	834 ± 1887	1768 ± 2594	431 ± 929	2792 ± 3919	N/A	2647 ± 2173	919 ± 2458
Diagnostic laboratory testing cost (mean ± STD)	825 ± 1104	1331 ± 1772	639 ± 630	1948 ± 2126	N/A	1905 ± 1600	756 ± 1006
ME-related laboratory tests (mean ± STD)	204 ± 234	213 ± 222	202 ± 211	501 ± 516	N/A	474 ± 451	163 ± 222
	Children (1–17 years)						
	Total[b]	Bacteria	Enterovirus	Herpes virus[c]	Arbovirus	Other virus	Unknown pathogens
Number of unique patients	3635	311 (8.6%)	2131 (58.6%)	50 (1.5%)	36 (1%)	12 (0.3%)	977 (26.9%)
Hospitalization cost (mean ± STD)	11,119 ± 34,904	21,961 ± 38,853	5842 ± 7376	30,906 ± 33,930	15,442 ± 10,141	29,676 ± 46,077	17,629 ± 59,267
Cost incurred till LP (mean ± STD)	3097 ± 3021	4117 ± 3966	2682 ± 1935	5042 ± 4160	4890 ± 5115	6413 ± 4377	3426 ± 4080
Patients with ICU stay *n* (%)	504 (13.9%)	96 (30.9%)	161 (7.7%)	17 (34%)	18 (50%)	7 (58.3%)	185 (18.9%)
ICU-related cost (mean ± STD)	30,631 ± 76,482	27,074 ± 42,970	10,652 ± 13,784	33,932 ± 31,077	13,743 ± 8817	38,485 ± 50,601	50,632 ± 114,577
Total medication cost (mean ± STD)	1771 ± 9965	2873 ± 7246	718 ± 2761	4631 ± 7449	3408 ± 6487	4727 ± 7236	3401 ± 17,108
Diagnostic laboratory testing cost (mean ± STD)	855 ± 2136	1285 ± 2248	552 ± 603	2246 ± 2794	1594 ± 1768	1936 ± 1992	1277 ± 3654
ME-related laboratory tests (mean ± STD)	172 ± 239	197 ± 255	149 ± 162	463 ± 550	222 ± 292	247 ± 214	195 ± 321

N/A = not applicable; STD = standard deviation.
[a] 54 patients were discharged with non-ME diagnosis.
[b] 115 patients were discharged with non-ME diagnosis and excludes 3 patients with fungal infection.
[c] HSV 1/2, VZV, CMV, HHV6.

testing cost and the fact that the mean PCR cost was $140 and, in this patient population, HSV PCR should have been ordered, we conclude that most of the institutions relied on reference laboratories whose testing costs were not captured in this database.

While it is well known that the use of molecular assays has not only a high sensitivity but a quicker turnaround time, the use of PCR in our study was 12.7% and 10.2% for infants and children, respectively (Table 1). The data suggest that for, the majority of cases, the diagnosis was either made clinically or the molecular tests were not captured because they were referred to a reference lab. The use of a multiplex rapid assay would provide improved guidance for patient management with fewer requests for other diagnostic testing. The use of rapid diagnostic tools is linked to improved clinical outcomes, resulting in a lower length of stay and cost (Bauer et al., 2010; Timbrook et al., 2017). Most of the standard of care for diagnosis of ME, such as CSF glucose and protein, is not always specific in predicting the pathogen causing the infection, and if the patient has been treated with antibiotics for more than 8 h prior to LP, the cultures will be sterile. Further, most of the tests require a long turnaround time before results are available (Kanegaye et al., 2001; Michael et al., 2010). Quick and accurate identification of the causative agent can be accomplished by the use of molecular technology. In the US, an FDA-approved real-time multiplex assay for the detection of pathogens from the CSF is the FilmArray® Meningitis/Encephalitis (ME) panel (bioMérieux/BioFire, Salt Lake City, UT) (Leber et al., 2016). The use of FilmArray® ME has shown an enhanced identification of Group B *Streptococcus* and *Escherichia coli* in infants (Arora et al., 2017) and may play a role in evaluating neonates for CNS infection, possibly resulting in shorter length of stay and reduced antimicrobial exposure among those with low-risk viral infection (Blaschke et al., 2018). Furthermore, it has been shown to enhance identification in patients with meningitis and a negative Gram stain (Wootton et al., 2016). Rapid identification of the agent causing ME is an asset in determining whether or not to initiate treatment. There is a potential cost reduction in direct antibiotic utilization when the FilmArray® ME panel is used, which is able to offset the increased cost of testing (Soucek et al., 2017). Likewise, Duff et al. (2018) described the potential cost savings predicted by a comprehensive modeled analysis using the FilmArray® ME rather than the standard of care.

Our study has a few limitations. It is a retrospective cohort study based on an administrative hospital discharge database. The ME diagnosis and pathogen categories were based on ICD-9 diagnosis codes. Coding errors or misdiagnosis by clinicians may lead to misclassification, but if that was the case, the level of misclassification should be similar across pathogen groups. Due to major differences in coding of the tests, not all were able to be included, especially if those tests were performed in different facilities. The study was designed to include all results; however, the complexity of recording could result in exclusion, but they would be evenly distributed between categories and likely not affect the proportion estimates. In conclusion, our study shows that, on average, the total visit costs were $12,759 for infants and $11,119 for children and that the cost increased if LP procedure was delayed, if ICU stay was needed, and if the etiology was viral other than arbovirus or enterovirus or bacteria.

Acknowledgment

This work was supported by Medical Affairs – Americas, bioMérieux.

References

Arora HS, Asmar BI, Salimnia H, Agarwal P, Chawla S, Abdel-Haq N. Enhanced identification of group B Streptococcus and Escherichia coli in young infants with meningitis using the Biofire Filmarray Meningitis/Encephalitis Panel. Pediatr Infect Dis J 2017;36:685–7.
Bauer KA, West JE, Balada-Llasat JM, Pancholi P, Stevenson KB, Goff DA. An antimicrobial stewardship program's impact with rapid polymerase chain reaction methicillin-resistant Staphylococcus aureus/S. aureus blood culture test in patients with S. aureus bacteremia. Clin Infect Dis 2010;51:1074–80.
Beckham JD, Tyler KL, Idsa. Initial management of acute bacterial meningitis in adults: summary of IDSA guidelines. Rev Neurol Dis 2006;3:57–60.
Blaschke AJ, Holmberg KM, Daly JA, Leber AL, Dien Bard J, Korgenski EK, et al. Retrospective evaluation of infants aged 1 to 60 days with residual cerebrospinal fluid (CSF) tested using the FilmArray Meningitis/Encephalitis (ME) Panel. J Clin Microbiol 2018;56(7):1–9.

Castelblanco RL, Lee M, Hasbun R. Epidemiology of bacterial meningitis in the USA from 1997 to 2010: a population-based observational study. Lancet Infect Dis 2014;14:813–9.
Davis KL, Misurski D, Miller JM, Bell TJ, Bapat B. Cost of acute hospitalization and post-discharge follow-up care for meningococcal disease in the US. Hum Vaccin 2011;7:96–101.
Duff S, Hasbun R, Ginocchio CC, Balada-Llasat JM, Zimmer L, Bozzette SA. Economic analysis of rapid multiplex polymerase chain reaction testing for meningitis/encephalitis in pediatric patients. Future Microbiol 2018;13:617–29.
Halpern NA, Pastores SM. Critical care medicine in the United States 2000–2005: an analysis of bed numbers, occupancy rates, payer mix, and costs. Crit Care Med 2010;38:65–71.
Hasbun R, Bijlsma M, Brouwer MC, Khoury N, Hadi CM, van der Ende A, et al. Risk score for identifying adults with CSF pleocytosis and negative CSF Gram stain at low risk for an urgent treatable cause. J Infect 2013;67:102–10.
Holmquist L, Russo CA, Elixhauser A. Meningitis-related hospitalizations in the United States, 2006: statistical brief #57. Healthcare Cost and Utilization Project (HCUP) statistical briefs (Rockville (MD)); 2006.
Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar puncture in pediatric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. Pediatrics 2001;108:1169–74.
Khoury NT, Hossain MM, Wootton SH, Salazar L, Hasbun R. Meningitis with a negative cerebrospinal fluid Gram stain in adults: risk classification for an adverse clinical outcome. Mayo Clin Proc 2012;87:1181–8.
Leber AL, Everhart K, Balada-Llasat JM, Cullison J, Daly J, Holt S, et al. Multicenter evaluation of BioFire FilmArray Meningitis/Encephalitis Panel for detection of bacteria, viruses, and yeast in cerebrospinal fluid specimens. J Clin Microbiol 2016;54:2251–61.
MacNeil JR, Bennett N, Farley MM, Harrison LH, Lynfield R, Nichols M, et al. Epidemiology of infant meningococcal disease in the United States, 2006–2012. Pediatrics 2015;135:e305–11.
Michael B, Menezes BF, Cunniffe J, Miller A, Kneen R, Francis G, et al. Effect of delayed lumbar punctures on the diagnosis of acute bacterial meningitis in adults. Emerg Med J 2010;27:433–8.
Nigrovic LE, Fine AM, Monuteaux MC, Shah SS, Neuman MI. Trends in the management of viral meningitis at United States children's hospitals. Pediatrics 2013;131:670–6.
Ramers C, Billman G, Hartin M, Ho S, Sawyer MH. Impact of a diagnostic cerebrospinal fluid enterovirus polymerase chain reaction test on patient management. JAMA 2000;283:2680–5.
Richie MB, Josephson SA. A practical approach to meningitis and encephalitis. Semin Neurol 2015;35:611–20.
Romero JR, Newland JG. Viral meningitis and encephalitis: traditional and emerging viral agents. Semin Pediatr Infect Dis 2003;14:72–82.
Shukla B, Aguilera EA, Salazar L, Wootton SH, Kaewpoowat Q, Hasbun R. Aseptic meningitis in adults and children: diagnostic and management challenges. J Clin Virol 2017;94:110–4.
Soucek DK, Dumkow LE, VanLangen KM, Jameson AP. Cost Justification of the BioFire FilmArray Meningitis/Encephalitis Panel versus standard of care for diagnosing meningitis in a community hospital. J Pharm Pract 2017 Jan 1:1–5. [897190017737697].
Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Lynfield R, Hadler JL, et al. Bacterial meningitis in the United States, 1998–2007. N Engl J Med 2011;364:2016–25.
Timbrook TT, Morton JB, McConeghy KW, Caffrey AR, Mylonakis E, LaPlante KL. The effect of molecular rapid diagnostic testing on clinical outcomes in bloodstream infections: a systematic review and meta-analysis. Clin Infect Dis 2017 Jan 1;64:15–23.
Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008;47:303–27.
Van TT, Mongkolrattanothai K, Arevalo M, Lustestica M, Dien Bard J. Impact of a rapid herpes simplex virus PCR assay on duration of acyclovir therapy. J Clin Microbiol 2017;55:1557–65.
Whitley RJ, Lakeman F. Herpes simplex virus infections of the central nervous system: therapeutic and diagnostic considerations. Clin Infect Dis 1995;20:414–20.
Wootton SH, Aguilera E, Salazar L, Hemmert AC, Hasbun R. Enhancing pathogen identification in patients with meningitis and a negative Gram stain using the BioFire FilmArray((R)) Meningitis/Encephalitis panel. Ann Clin Microbiol Antimicrob 2016;15:26–9.