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Economic Evaluation: Onsite HSV PCR Capabilities for Pediatric Care

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ABSTRACT

Objective: Herpes simplex virus (HSV) encephalitis has an overall mortality rate of 11%–29% with treatment. Although rare, HSV encephalitis is frequently tested for and empirically treated, especially in the neonatal population. HSV infection can be diagnosed with polymerase chain reaction (PCR) testing, although this frequently requires sending samples to reference laboratories. The inherent delay in results may lead to prolonging empiric treatment and hospital stay, resulting in increased costs. This study investigates whether onsite HSV PCR testing decreases hospitalization duration, acyclovir treatment duration, and financial cost on an institution. **Project design:** This single-center project utilized the IHI model for improvement to evaluate third-party HSV PCR processing versus an implemented onsite PCR-based meningitis–encephalitis panel for HSV central nervous system evaluation. The primary outcome was hospital cost differential with secondary outcomes, including duration of acyclovir administration and time to result. **Results:** We identified 96 children age 0–18 from 2010 to 2016, 74 patients utilizing offsite third-party testing, and 22 patients utilizing onsite. We observed a per-patient cost savings of $428 ($618.43–$190.43, $P = 0.029$) upon the implementation of onsite testing. The mean duration of acyclovir therapy decreased from 3.7 to 0.26 days per patient ($P < 0.001$). Time to result decreased from 4.6 to 0.13 days ($P < 0.001$). **Conclusions:** Acquisition of real-time local HSV PCR capabilities significantly decreased time to result and empiric medication use while significantly reducing hospital costs in a military treatment facility. *(Pediatr Qual Saf 2020;2:e266; doi: 10.1097/pq9.0000000000000266; Published online March 10, 2020.)*

INTRODUCTION

Herpes simplex virus (HSV) is an etiologic agent of serious central nervous system (CNS) infection in both adults and children. HSV encephalitis has an overall mortality rate of 11%–29% with treatment.[1–3] Maternal HSV infection may result in neonatal disease, which includes disseminated skin, eye, and mouth, and CNS infection. A recent study shows neonatal HSV rates in the United States increased from 7.9 to almost 10 in 100,000 births between 2003 and 2014, with an average total hospital cost of $29,463 US dollars.[4] Delayed treatment with high-dose acyclovir is associated with higher inpatient morbidity and mortality.[5,6]

Although rare, HSV infection is frequently tested for and empirically treated, incurring upon the healthcare system considerable financial and medical costs. Laboratory testing is crucial in confirming the diagnosis. The viral culture was the previous gold standard, with positive growth anticipated within 24–48 hours of testing.[3,7,8] Reported sensitivities for viral culture vary greatly from 94% for eye and skin cultures, 48% for oral cultures, to 40% in CNS or disseminated disease states.[1]

Polymerase chain reaction (PCR) testing is comparatively a more expedient and sensitive method for detecting CNS disease and serves as the new gold standard and is preferred over viral culture.[9,10] It features an overall time to result within 2 hours, with a sensitivity of approximately 95%, and a specificity ranging from 71% to 100%.[11] PCR testing may also detect asymptomatic viral shedding seen in early HSV encephalitis and as well as throughout the first week of antiviral therapy. Unfortunately, HSV PCR testing often requires a third-party laboratory and subsequent prolonged acyclovir exposure and inpatient hospitalization, which impose a significant financial burden.

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As a result, multiple institutions have limited HSV PCR testing to patients with pleocytosis on cerebrospinal fluid (CSF) studies.[12] However, this practice can lead to delay in diagnosis of HSV CNS disease as the virus can be present in the absence of pleocytosis.[13–16]

Recently, Van et al[17] have shown that real-time onsite HSV PCR can decrease time to laboratory result as well as overall acyclovir use in the pediatric and adult populations; however, this study did not specifically address costs. Additional studies have shown that the use of the BioFire Meningitis–Encephalitis (ME) panel potentially reduces hospitalization costs in adults.[18] The most recent cost analysis of real-time HSV CSF PCR was in 2010 by Shah et al,[19] which showed the increased length of hospital stay with referral testing. There are no other recent cost analyses of real-time PCR of HSV in pediatric patients published outside of proposed models looking at treatment with and without pleocytosis versus empiric treatment without testing.[20]

This process improvement project was designed to compare a previous standard of third-party HSV PCR testing to onsite use of the BioFire FilmArray ME molecular diagnostics panel for HSV CNS testing (BioFire Diagnostics, Salt Lake City, Utah), evaluating time to diagnosis, days of intravenous acyclovir utilization, the cost associated with acyclovir, and overall cost of care.

METHODS

Target Population

We targeted neonatal and pediatric patients undergoing evaluation of HSV in CSF samples for this process improvement project. We defined neonatal patients as infants 28 days of age or less at the time of evaluation. Pediatric patients were defined as 29 days to less than 18 years of age. All patients in the study were beneficiaries of the military health system. The institutional review board reviewed this quality improvement project with nonresearch quality improvement designation.

Setting

The Brooke Army Medical Center (BAMC) is a tertiary care military hospital with 425 total beds, 51 pediatric beds consisting of a 24-bed neonatal ICU (NICU), a 6-bed pediatric ICU (PICU), and a 25-bed pediatric ward. Stakeholders of the project included staff pediatricians, neonatologists, pediatric residents, neonatal fellows, and registered nurses working in the PICU, pediatric ward, NICU, and the molecular laboratory.

Study Perspective

The project goals were to shorten time to test results, thereby reducing unnecessary hospital duration, days of intravenous acyclovir utilization, cost-associated with acyclovir, as well as reduce the overall cost of care. We developed the project in response to concerns that a population of patients was experiencing prolonged antiviral therapy and hospital stay due to the delay in turnaround time when shipping isolates out to third party laboratories. We aimed to demonstrate that real-time PCR capabilities and improved result times would offer economic benefits in the form of decreased antiviral drug use and hospital stays that would collectively offset the new startup laboratory operational and instrument costs. The A3 tool shown in Figure 1 is our visual representation of our IHI process improvement development.

Comparators

This process improvement compared the cost of a hospital stay directly related to delays in CSF assays sent for outside laboratory HSV PCR versus the cost of a hospital stay directly related to real-time HSV PCR on CSF. Secondary measure evaluated if the savings offset the startup costs of obtaining new laboratory instruments and assays.

We implemented the BioFire FilmArray ME Panel in the BAMC Molecular Laboratory Department. The panel is a comprehensive multiplex PCR with a 94.2% sensitivity and 99.8% specificity for the detection of 14 pathogens associated with CNS infection, inclusive of HSV-1 and HSV-2 (100% specificity and 99.9% sensitivity).[21,22] Postimplementation, all patients with suspected HSV CNS infection had CSF tested utilizing the device onsite. We completed internal validation in 2016 before utilization.

Time Horizon

We completed a retrospective chart review of all pediatric patients who had at least one or more CSF assays sent for outside laboratory HSV PCR during admission to the facility between January 1, 2010, and December 31, 2015, designated as the pre-ME panel study group. The post-ME panel study group encompassed all pediatric inpatients under clinical suspicion for active HSV disease from January 1, 2016, to August 31, 2016, who received HSV PCR laboratory evaluation of CSF following the implementation of the ME panel.

Choice of Health Outcomes

Our facility aimed to decrease HSV PCR processing time from the baseline median 3.7 days to less than 24 hours without incurring extensive additional facility cost.

Measurement of Effectiveness (Single Study-based Estimate)

The primary outcomes of the process improvement measured time to result of HSV CSF PCR. Balancing measures were the cost differential as defined per patient and total hospital cost, including the implementation cost comparing the third party and onsite laboratory processing. Secondary outcomes included the number of days of acyclovir administration and the total cost of acyclovir therapy. We evaluated each patient chart for PCR time to result, the number of acyclovir doses received, total acyclovir cost and days of extended inpatient stay pending time to result. Prolongation of hospital stay was defined as continued antiviral therapy after bacterial meningitis

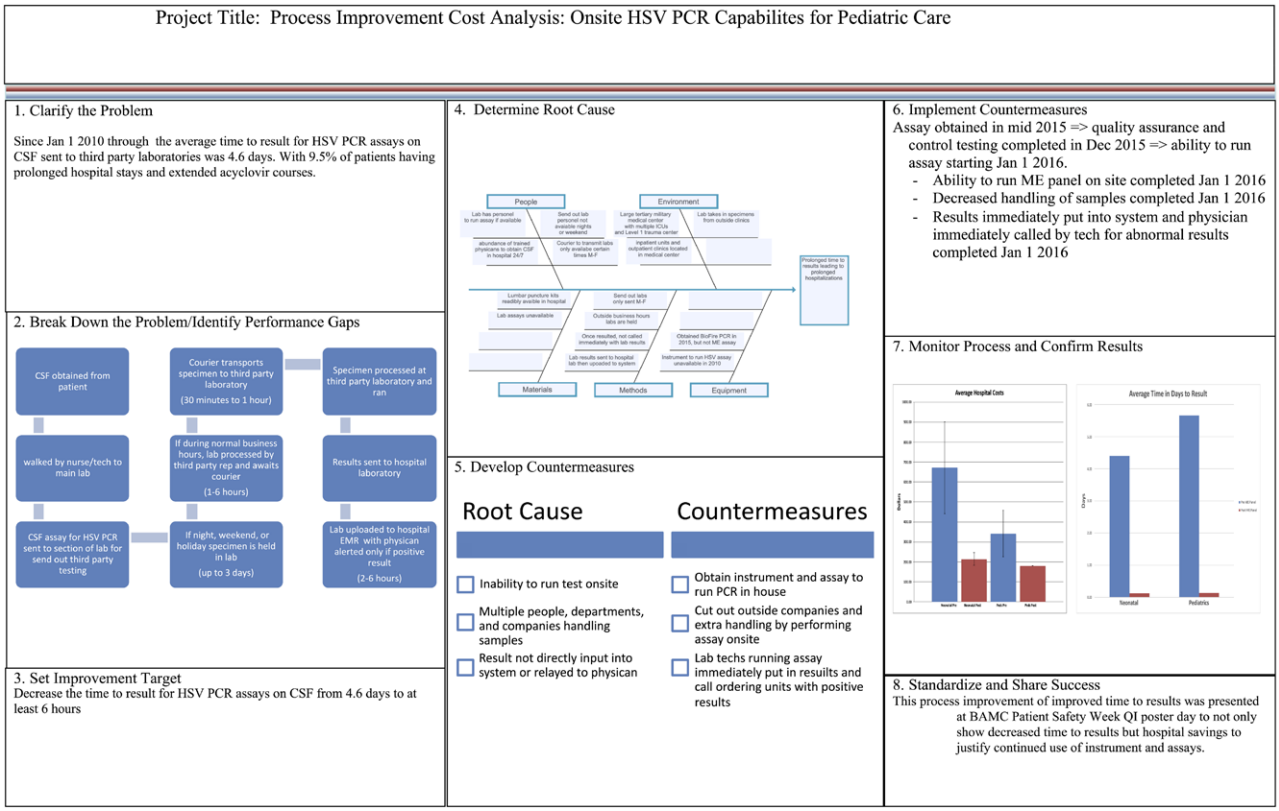

Fig. 1. A3 visual road map of our eight step Institute for Healthcare Improvement (IHI) process improvement development.

was ruled out (or thought to be highly unlikely given laboratory data and clinical status), discontinuation of any antibacterial therapy, and the patient meeting discharge criteria per the attending physician. We did not use concomitant CSF cell, protein, and glucose counts to triage pediatric patients before the ME panel completion as in prior adult studies.[23] This decision is based on the lack of consistent pleocytosis, especially in neonates.[24]

Statistical Cost Analysis

We performed a cost analysis to evaluate the process improvement between the 2 time periods. We calculated the following costs and included them in the analysis: cost per hospital day (varied by inpatient unit), cost of reagents for the ME panel, the total cost for third-party HSV PCR, and cost of acyclovir antiviral therapy (Table 1). The BioFire FilmArray instrument costs were not included in the per-patient cost analysis as our facility already used this instrument for other molecular testing (respiratory viruses by PCR) before ME panel implementation. However, a break-even analysis (including instrument and software costs shown in Table 1) was performed to determine the number of total cases needed before cost savings were achieved. There were no identified additional costs for performing the ME panel, such as the requirement for additional personnel, extensive training cost, or high costs of maintenance of the instrument per laboratory. The costs were directly compared using a 2-tailed unequal variance *t* test due to population heterogeneity. We completed all calculations using Microsoft Office Excel (Microsoft Corporation, Redman, Wash.).

Table 1. Cost Estimates Utilized to Generate Cost Analysis

One-time Cost	USD
FilmArray	$35,804.02
Software	$1,989.95
Total	$37,793.97
Per patient tested	
ME panel (onsite)	$180.00
HSV PCR (third party)	$80.00
Hospitalization	(Mean/Day)
NICU	$2,418.87
Pediatric ward	$1,116.54
PICU	$2,814.18
Well newborn	$666.20
Medication	(Cost/Dose)
Acyclovir	$15.00
Total savings per patient (mean)	$420.55
Patient No. to break even (NNT)	90

Summarization of cost estimates in US dollars for instrument cost, cost per test, and cost per unit day

Assumptions

Assumptions made for this study were that all costs were the same for a hospital bed in each unit, and the third-party HSV assay costs remained the same throughout the study period.

RESULTS

A total of 108 patients were included for review, 74 pre-ME and 34 post-ME. The characteristics of the patients included in the study are shown in Table 2. We excluded patients transferred from the facility (n = 1 post-ME), lost samples (n = 2 pre-ME), samples drawn by other sites before admission (n = 1 post-ME), and treatment despite several negative tests (n = 1 post-ME), for a total of 72 pre-ME and 31 post-ME. We included patients with other disease states identified by the ME panel (n = 9). There was not a significant difference between the groups when considering suspected (culture-negative sepsis) and proven infection (viral, bacterial, and pneumonia) versus noninfectious with an OR 0.84 (95% confidence interval: 0.34, 2.1).

Before the implementation of the ME panel, 9.5% of patients had a prolonged hospital stay with empiric acyclovir therapy while awaiting PCR results, costing, on average, an extra $420.55 ($618.43 pre-ME to $197.88 post-ME, $P = 0.032$) more per patient (Table 1). When the duration of hospitalization and empiric acyclovir use costs are extrapolated, the hospital break-even point of startup costs was after 90 negative tests. Secondary outcomes of time to result (4.6 versus 0.16 days, $P < 0.001$) and duration of acyclovir therapy (3.7 versus 0.26 days, $P < 0.001$) per patient were all reduced (Table 3).

Onsite HSV testing had the greatest impact on the neonatal population (Table 3). Hospital costs decreased on average, from $671.12 pre-ME to $214.29 post-ME ($P = 0.05$). Time to result decreased from 4.41 to 0.13 days ($P \leq 0.001$). The duration of acyclovir use was also reduced from 3.78 to 0.85 days ($P \leq 0.001$).

The pediatric (nonneonatal) population was significantly impacted only in time to result and duration of acyclovir therapy (Table 3). On average, hospital costs were decreased from $341.80 pre-ME to $191.25. However, this decrease did not reach statistical significance ($P = 0.21$). Time to HSV PCR results decreased from 5.67 to 0.17 days ($P = 0.017$). The duration of acyclovir was reduced from 3.75 to 0.25 days ($P = 0.05$). One pediatric patient with enterovirus meningitis received empiric acyclovir, whereas the rest of the patients did not, due to either the team either awaiting ME panel results (all negative for HSV) or negative results returning by the time medications were available to administer.

DISCUSSION

We were able to successfully implement a process improvement project targeting a reduction in time to HSV PCR testing results while effectively decreasing hospital costs in our facility. Our study supports the use of localized PCR testing by reporting reduced hospitalization and acyclovir exposure in the pediatric population. This project potentially represents the first process improvement project to show improvement in hospital costs of onsite CSF HSV PCR testing for the pediatric population alone.

All patients in this study had further work-up outside of HSV testing, to include bacterial cultures of the CSF and blood. Positive cultures are noted in Table 3. In most of these cases, acyclovir was discontinued once an alternative infectious etiology was determined in a pre-ME panel group, even if the HSV PCR did not result at that time per the attending on chart review. Per our definition of prolonged hospitalization, these patients did not meet

Table 2. Patient Characteristics

	<28 Days		29 Days–12 Months		1–5 Year		6–17 Years	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
NICU	47	9						
Pediatric ward	9	0	4	5	1	2	3	10
PICU	4	0	3	4	0	0	1	1
Discharge diagnosis								
Bacterial meningitis*	2	1	2	0	0	0	0	0
Viral meningitis†	1	1	1	3	0	0	0	4
Culture positive sepsis‡	3	0	0	0	0	0	0	0
Culture negative sepsis	6	1	0	0	0	0	0	0
HSV viremia/meningitis	0	0	1	0	0	0	0	0
R/O HSV	2	0	0	0	0	0	0	0
Pneumonia	6	0	0	0	0	0	0	0
RDS	6	0	0	0	0	0	0	0
Neurological	8	1	1	1	0	0	0	3
Hypothermia	3	1	0	0	0	0	0	0
Apnea	8	1	0	0	0	0	0	0
Fever	9	0	1	3	0	1	1	1
Other	6	3	1	2	1	1	3	3

Demographics of patients undergoing HSV evaluation.

*Bacterial meningitis included GBS (n = 2) and *Escherichia coli* (n = 2) in the pre-ME group and GBS (n = 1) in the post-ME group.

†Viral meningitis included enterovirus (n = 2) in the pre-ME group and enterovirus (n = 6), cytomegalovirus (n = 1), human herpesvirus 6 (n = 1) in the post-ME group.

‡Positive blood cultures included GBS (n = 1), *Escherichia coli* (n = 1), Coagulase negative staph (n = 1). Other diagnoses were defined as diagnoses that were made only once these included neutropenic fever, BRUE/ALTE, hypoglycemia, PPHN, TTN, cellulitis, URI, and unknown etiology.

BRUE/ALTE, brief resolved unexplained event/apparent life-threatening event; GBS, group B streptococcus; PPHN, persistent pulmonary hypertension of the newborn; TTN, transient tachypnea of the newborn; URI, upper respiratory infection.

Table 3. Outcomes of Hospital Cost, Time to Results, and Acyclovir Treatment

Total Hospital Cost ($USD)		Mean	95% CI	*P*
	Pre-ME	618.43	(241.14–995.29)	
Total	Post-ME	197.88	(175.23–220.53)	0.032
Neonatal	Pre-ME	671.12	(220.21–1122.03)	0.05
	Post-ME	214.29	(164.48–264.10)	
Pediatric	Pre-ME	341.80	(122.28–561.32)	0.21
	Post-ME	191.25	(166.47–216.03)	
Time to results (Days)				
Total	Pre-ME	4.60	(3.54–5.37)	<0.001
	Post-ME	0.16	(0.068–0.25)	
Neonatal	Pre-ME	4.41	(3.57–5.25)	<0.001
	Post-ME	0.13	(0.11–0.15)	
Pediatric	Pre-ME	5.67	(1.82–9.52)	0.017
	Post-ME	0.170	(0.13–0.21)	
Days of acyclovir				
Total	Pre-ME	3.77	(3.10–4.44)	<0.001
	Post-ME	0.26	(–0.24 to 0.76)	
Neonatal	Pre-ME	3.78	(3.23–4.33)	<0.001
	Post-ME	0.85	(–0.25 to 1.95)	
Pediatric	Pre-ME	3.75	(0.61–6.89)	0.05
	Post-ME	0.25	(–0.21 to 0.71)	

Summarization of outcomes broken down by group.
*A statistically significant difference between groups (*P* value less than 0.05).

this qualification because they were continuing treatment for bacterial etiologies. All neonates with suspected HSV infection received additional evaluation per the AAP Red Book (to include surface swabs and blood PCR in infants in the NICU).[7] No patients presented with cutaneous lesions requiring PCR or culture.

It is worth noting that in the pre-ME panel group, the average time to test result was longer than the average acyclovir duration. As noted earlier, we gathered this information via retrospective chart review, and, in some cases, acyclovir was discontinued before HSV laboratory testing returned due to either confirmation of bacterial etiology or otherwise low clinical suspicion of disease by the attending pediatrician. This likely contributed to our lower than expected prolonged hospitalizations in the pre-ME group.

This project demonstrated that decreased time to result directly led to decreased acyclovir exposure in our population. Additional benefits of decreased high-dose acyclovir exposure include the reduction of potential side effects like neutropenia, nephrotoxicity, neurotoxicity, and allergic reactions.[6,25] Neutropenia and nephrotoxicity are the more common adverse side effects, occurring at reported rates of 21% and 6%, respectively.[26] We did not include these outcomes in this process improvement project, but theoretically, they contribute to additional reductions in medical costs.

The concomitant requirement of dedicated intravenous access in the administration of acyclovir treatment serves as an additional factor affecting decreases in costs and patient harm, also not quantitatively accounted for in this project. We would expect a decrease in the peripheral catheter and peripheral-inserted central catheter (PICC) use with our achieved decreased acyclovir therapy duration. Catheter placement attempts and the need for PICC placement were unable to be determined through chart review and were thus excluded from calculated hospital costs. Qualitatively, inherent cost considerations associated with these procedures include medical costs related to sedation risks and complications such as infection, thrombosis, and phlebitis. Further financial costs are incurred with specially trained nursing staff required for PICC placement as well as NICU admission for neonates.

Limitations

A major limitation of this process improvement project was that it took place in a single-payer system within the Department of Defense. In this system, hospital days, medication costs, and laboratory costs may not reflect other payer reimbursement schedules. This study also does not investigate the cost savings for patients and families due to the structure of the military health system. Nevertheless, the decrease in time to results and hospital days are expected to translate to increased savings for patients. It is also important to note that the NICU at BAMC is a "clean unit," meaning all admissions from the clinic or the emergency department is admitted to the pediatric ward or the PICU even if under 30 days of age. Consideration of the admitting unit was taken for cost analysis, as shown in Table 2.

Another potential limitation of our study is its lack of analysis of other capabilities of the BioFire ME panel, which tests for 14 pathogens implicated in meningitis: *Escherichia coli* K1, *Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae* (GBS), *Streptococcus pneumoniae,* cytomegalovirus, *enterovirus,* human herpesvirus 6, human parechovirus, varicella zoster virus, and *Cryptococcus neoformans/gattii*. Although we detected no positive HSV infections in the post-ME group, we observed nine samples positive for other pathogens, as shown in Table 2. Although not assessed in this improvement project, the availability of such a sensitive and rapid broad-spectrum molecular assay would be expected to offer similar benefits to the empiric treatment of other suspected pathogens.

CONCLUSIONS

Real-time local HSV PCR capabilities significantly decreased time to result and empiric antiviral use while significantly reducing hospital costs in a military treatment facility. Medical facilities with dedicated pediatric and neonatal care should consider procuring onsite HSV PCR processing to decrease time to result and potential unnecessary acyclovir treatment.

DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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