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Maj Nicholas R Carr

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59th Clinical Research Division
1100 Willford Hall Loop, Bldg 4430
JBSA-Lackland, TX 78236-9908
210-292-7141

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59th Clinical Research Division
1100 Willford Hall Loop, Bldg 4430
JBSA-Lackland, TX 78236-9908
210-292-7141

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In-House HSV PCR, Process Improvement and Cost-Effectiveness Analysis

Zachary J. Weber, DO, Nicholas R. Carr, DO, Deena E. Sutter, MD
Department of Pediatrics, Brooke Army Medical Center, San Antonio, Texas

BACKGROUND

Herpes Simplex Virus (HSV) is an etiologic agent of serious central nervous system (CNS) infections in both adults and children. HSV encephalitis has a worldwide incidence of about 500,000 persons per year with an overall mortality rate of 11-19% with treatment. Maternal HSV infection may result in neonatal disease, to include disseminated, skin eye and mucous membrane (SEM) and CNS infection. Neonatal HSV infections occur approximately in 1 in 3000 to 20,000 live births with about 1500 cases reported annually with 29% mortality with aggressive treatment.

Laboratory testing is crucial in confirming the diagnosis. Culture is the traditional standard, especially for skin, eyes mouth disease (SEM) evaluation, with positive growth usually occurring with 24-48 hours of testing. However, PCR testing is not only a more expedient (1-2 hours) but also sensitive test for detecting CNS disease (Sn 95%), with overall specificity ranging from 71 – 100%. PCR testing may also detect asymptomatic viral shedding. PCR results return positive early in the course of HSV encephalitis and remain positive during the first week of therapy.

While rare, HSV is tested for frequently and empirically treated. HSV carries significant financial and medical costs for these reasons. HSV can be diagnosed with PCR; most testing takes place at non-local facilities, often prolonging acyclovir exposure and hospital stay.

Our institution has relied on outside reference laboratories for PCR diagnosis of HSV CNS infection. We historically noted numerous occasions when pediatric patients were hospitalized for several days while awaiting results of HSV PCR testing. We determined overall time to HSV PCR results ("pre-ME panel") and total doses/cost of acyclovir for those patients, and recommended implementation of a in-house PCR assay for the detection of HSV1 and HSV 2.

QUALITY IMPROVEMENT PROCESS

This project was conducted as a Quality Improvement/Cost-Effectiveness analysis with the goal of reducing prolonged hospitalization, unnecessary medications and excess costs for pediatric patients receiving care at our institution.

The pre-intervention "pre-ME panel" group included pediatric and young adult patients (age 0-24 years) who had CSF assays sent for HSV PCR between Jan 2010 through December 2015. Total Pre-ME Panel population comprised 98 patients, including 62 neonates in the NICU, 11 pediatric patients (nursery discharge – 17 years), and 23 adults (18 – 23 years).

For this group, time to test results and duration of hospitalization (in days) was determined. Hospital duration (calculated by inpatient unit type), costs of HSV PCR testing and days of acyclovir were used to calculate estimated costs (see table 1). These data supported implementation of in-house PCR testing.

In December 2015 our molecular laboratory introduced and validated the Filmarray Meningitis/Encephalitis (ME) panel, (Biofire diagnostics) which is an FDA-cleared molecular panel. The ME panel is a multiplex PCR assay and includes 14 pathogens which may cause CNS infection, to include HSV-1, HSV-2.

Results from these samples were reported to providers as early as January 2016. Estimates on hospital stay, cost of acyclovir, costs of lab testing (ME panel) and hospital costs were calculated for patients who had the ME panel ordered from January-August 2016 (post-intervention period).

The post-intervention ("Post-ME Panel") implementation patient group included 33 patients, including 7 NICU, 15 pediatric ward (from nursery discharge – 17 years), and 10 adults (18 – 23 years).

The Filmarray instrument costs were not included in the per-patient cost analysis as this instrument was already used at our facility for other molecular testing (Respiratory Viruses by PCR). However, a break-even analysis (including instrument and software costs) was performed to determine the number of total cases needed before costs savings was achieved. There were no identified extra costs for performing the ME panel (such as requirement for additional personnel, extensive training cost) or significant costs of maintenance of the instrument per laboratory.

Table 1: OVERALL COSTS

Panel (reagents): $180.00	NICU per day: $2418.87
HSV PCR Send-out: $80.00	PICU per day: 2814.18
Average cost/dose acyclovir: $15.00	Peds Ward per day: $1116.54
	Nursery per day: $666.20
	Adult Ward per day: 1608.10

Start-up costs not included in per-patient cost analysis:
FilmArray (instrument): $35804.02*
ME Panel Software: $1989.95

*Instrument was already in use in molecular lab when ME panel was introduced

AVERAGE NUMBER OF DAYS TO RESULTS

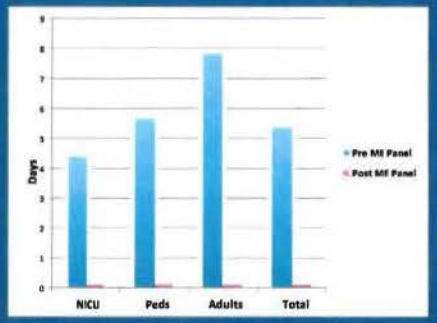

Figure 1 Average # days to results of HSV send out lab vs in house ME panel. $p = 0.016$ in pediatric population, $p < 0.001$ in all other populations

AVERAGE ACYCLOVIR COSTS

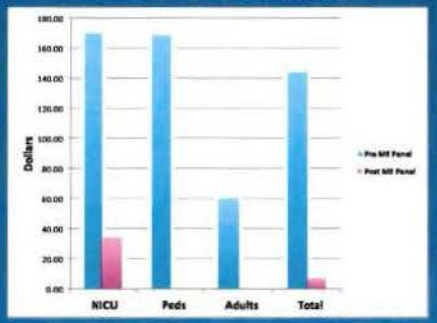

Figure 2 Average acyclovir cost in US dollars in patients waiting for HSV PCR results. $p < 0.001$ in NICU and total populations, $p = 0.405$ and $p = 0.099$ in adult and pediatric populations respectively.

AVERAGE NUMBER OF DAYS OF ACYCLOVIR

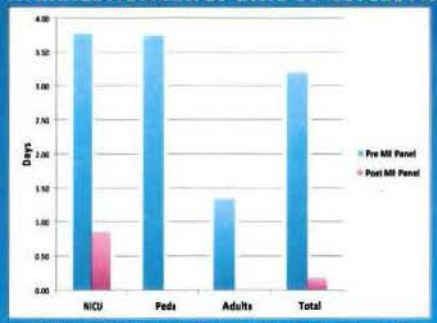

Figure 3 Average acyclovir use in days in patients waiting for HSV PCR results. $p < 0.001$ in NICU and total populations, $p = 0.089$ and $p = 0.099$ in adult and pediatric populations respectively.

AVERAGE EXTRA HOSPITAL COSTS WAITING ON RESULTS

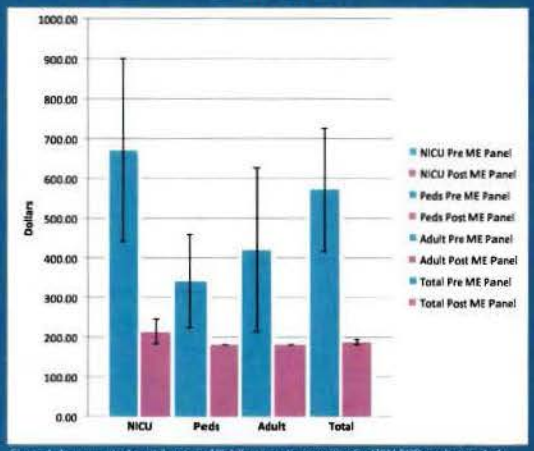

Figure 4 Average extra hospital costs in US dollars in patients waiting for HSV PCR results to include unit per hospital day, ME panel costs, HSV PCR send out costs, and acyclovir costs. $p = 0.05$ and $p = 0.014$ in NICU and total populations respectively. $p = 0.17$ and $p = 0.25$ in pediatric and adult populations respectively.

RESULTS

Prior to implementation of ME panel, 8% of patients had a prolonged hospital stay with empiric acyclovir therapy while awaiting PCR results costing on average $384.66 more per patient. The cost reduction was significantly decreased in the neonatal population ($p = 0.05$). The standard error of the mean (SEM) was used due to the small sample size and the large variation in hospital costs due to waiting for results to return. Of note, no patient had a positive CSF HSV PCR result.

Average time to results decreased from 5.36 days to 3.1 hours ($p < 0.001$). Average duration of acyclovir therapy was 3.2 days per patient compared to 0.18 days per patient with in-house testing ($p < 0.001$).

When the decreased hospitalization and empiric acyclovir use costs are extrapolated, the hospital break-even point of start up costs was after 99 negative tests.

CONCLUSION

In house PCR capability conclusively shortens time to results, acyclovir usage, hospital duration and costs in the neonatal patient. In house processing should be considered in facilities with inpatient neonatal and pediatric care. It is especially useful in the neonatal population where infant suspected of HSV infections are empirically started on Acyclovir due to the high mortality rate. Presence of in-house HSV PCR testing has improved care by reducing duration of hospitalization, unnecessary antiviral therapy and reduces overall costs in patients with suspected HSV CNS infection.

For additional information please contact:
Zachary Weber, DO
Dept of Pediatrics, San Antonio Military Medical Center, San Antonio, TX
Zachary.j.weber9.mil@mail.mil