Availability of 24/7 Rapid HSV PCR Test Directly Impacts Acyclovir Exposure in Pediatric Patients

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ABSTRACT (revised)

Objectives: Herpes simplex virus (HSV) infection of the central nervous system (CNS) is associated with significant morbidity and mortality in children. Current guidelines recommend early treatment of all suspected HSV CNS infection with intravenous acyclovir and to perform diagnostic testing. Testing of cerebrospinal fluid (CSF) for HSV by polymerase chain reaction (PCR) is currently the diagnostic method of choice. Ruling out HSV CNS infection is also important as it allows for discontinuation of acyclovir and avoidance of unnecessary drug costs and adverse reactions, including nephrotoxicity and inflammation. Turn-around-time (TAT) of HSV PCR is dependent on laboratory testing availability. This study assessed the impact of a Direct HSV (dHSV) PCR assay on acyclovir therapy in children suspicious for HSV CNS infection.

Methods: A pre- and post-implementation study was conducted on pediatric patients presenting to the Emergency Department at Children's Hospital Los Angeles (CHLA) with signs and symptoms of meningitis or encephalitis. A total of 208 patients with HSV PCR ordered on CSF were included in the retrospective analysis; 109 patients pre-implementation and 99 patients post-implementation. In the pre-implementation period, an indirect HSV (iHSV) PCR assay was performed six days a week, 9am to 5pm versus a dHSV PCR assay offered 24 hours a day, 7 days a week post-implementation. All results were reported in the electronic medical records. Medical chart review was performed to determine initiation and duration of acyclovir therapy.

Results: The patients ranged from 1 day to 22 years of age (mean: 3.2 years) with no significant differences in baseline demographics noted between the two groups. The vast majority of patients had no significant comorbidities (68%, pre-implementation; 67%, post-implementation). None of the patients were positive for HSV PCR from CSF, although HSV was detected from alternate sources in 7 additional patients, 2 of which were from blood. An additional 9 patients (4.3%) were diagnosed with meningitis due to Enterovirus (n=8) and Varicella-zoster virus (n=1). Implementation of dHSV PCR decreased average time to reporting from 23.2 h to 9.7 h ($p < 0.001$). Acyclovir therapy was initiated in 73 patients pre-implementation and 70 post-implementation and mean time to initiation was not significantly different between the two groups (pre: 6.9 h; post: 4.9 h; $p = 0.2$). In patients with negative HSV PCR, the mean time from collection to acyclovir discontinuation was 10.6 hours longer pre-implementation (26.5 h vs 15.9 h; $p < 0.001$). Two patients post-implementation avoided acyclovir therapy entirely due to availability of results prior to initiation.

Conclusions: Laboratory diagnosis of HSV CNS infections is imperative to the treatment and management of pediatric patients. Importantly, timely exclusion of HSV infection, through the availability of a 24/7 dHSV PCR test, allows for prompt discontinuation of acyclovir therapy, avoiding unnecessary costs and potential adverse reactions.

INTRODUCTION

- Herpes simplex virus (HSV) is a significant pathogen associated with a variety of infections ranging from localized infections of skin to disseminated disease with involvement of the central nervous system (CNS).
- Evaluation of cerebrospinal fluid (CSF) by PCR assay is the diagnostic test of choice for HSV meningitis/encephalitis. Current guidelines recommend initiation of empiric therapy on all patients suspicious of HSV infection, particularly encephalitis, as delay in therapy can significantly increase mortality rate.
- For cases of CNS infections, acyclovir is the drug of choice at 10mg/kg intravenously every 8 hours. Although usually well tolerated, some adverse effects, including neurotoxicity and renal dysfunction can occur with acyclovir therapy.
- As the vast majority of suspected cases of HSV meningitis/encephalitis are negative, it is imperative to provide negative result in a timely manner to minimize unnecessary exposure to acyclovir.

INTRODUCTION (Cont)

- Goals of study:
  - To determine the impact on turn-around-time (TAT) after implementation of a direct HSV (dHSV) PCR assay.
  - To determine the direct impact of rapid testing on acyclovir usage in pediatric patients seen at CHLA.

METHODS

- A total of 208 pediatric patients with with HSV PCR ordered on CSF sample were included in the study. Patients with unrelated, long-term medical conditions were excluded
- Pre-implementation:
  - Conventional HSV PCR testing was performed between 9am to 5pm, six days a week. Samples required nucleic acid extraction step and were batched once/day.
  - 109 patients were tested in this group.
- Post-implementation
  - Direct HSV PCR (dHSV) assay using the Simplexa™ HSV 1 & 2 Direct Kit (Focus Diagnostics) was performed 24 hours a day, 7 days a week. Separate nucleic acid extraction was not required and continuous testing was carried out.
  - 99 patients were tested in this group.
- The following analyses between the two groups were performed:
  - Basic demographics and co-morbidities
  - TAT of HSV PCR results
  - Time from specimen collection to halting acyclovir
  - Time from result reporting to halting acyclovir
- Statistical significances were calculated using the t-test.

Table 1. Characteristics of 208 patients from the pre- and post groups

	Pre-implementation (n = 109)	Post-implementation (n = 99)	P values
Mean age (range)	3.8 y (1 day - 21 years)	2.4 y (1 day - 22 years)	0.07
<30 days old (%)	30 (28%)	45 (45%)	0.14
Sex			
Male (%)	59 (54%)	60 (60%)	0.35
Female (%)	50 (46%)	39 (39%)	0.35
Co-morbidities (%)	35 (32%)	33 (33%)	0.85
Number of patient given acyclovir (%)	73 (67%)	70 (71%)	0.56
Median duration of acyclovir therapy for all patients (range)	26.4 h (5 min - 18 days)	13.3 h (1 min - 18 days)	0.15
Median duration of acyclovir therapy for HSV negative patients (range)	24.2 h (5 min - 18 days)	12.3 h (1 min - 9 days)	0.29
HSV Positivity (CSF & other sources) (%)	5 (4.6%)	2 (2%)	0.30
Other Etiologies (CSF) (%)	1 (0.9%)	8 (8.1%)	0.01

RESULTS

- 208 patients were enrolled in the study. The patients ranged from 1 day to 22 years (mean: 3.2 years) with no significant differences in demographics between the pre- and post implementation period (Table 1).
- HSV was detected from alternate sources in 7 patients, 2 of which were from blood (Table 1).
- Nine additional patients were diagnosed with meningitis, with CSF specimens positive for Enterovirus (n = 8) and Varicella-zoster virus (n = 1) (Table 1).
- Mean time from specimen collection to HSV PCR result was 13.5 h longer in the pre-implementation period (23.2 h vs 9.7 h, $p < 0.001$) (Figure 1). TAT ranged from 51 min - 5.1 d (pre) and 1.9 h - 43.5 h (post).
  - 81.7% of samples were reported in > 12 h pre-implementation compared to 45.5% reported in < 4 h post-implementation (Figure 2).
- In the post-implementation group, reporting distribution of HSV results were 56.6% between 8am-6pm and 43.4% between 8pm-6am (Figure 3).

Figure 1. Specimen Collection to Result Reporting

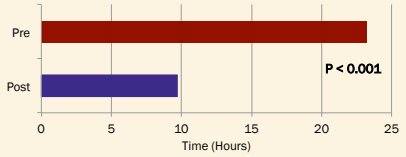


Figure 2. Time of Specimen Collection to Result Reporting

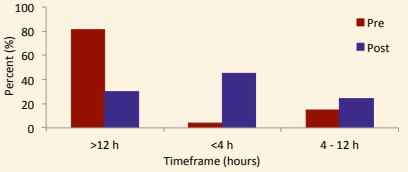
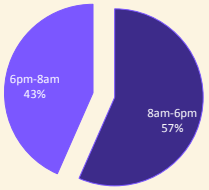


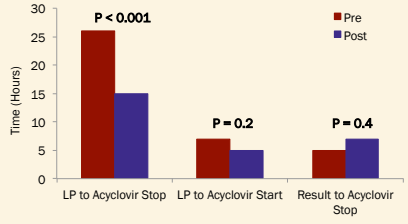
Figure 3. Reporting Distribution of Post-implementation Group



RESULTS

- Acyclovir was prescribed to 73 (67%) and 70 (71%) patients in the pre- and post-implementation groups, respectively (Table 1).
  - Median duration of therapy for all and for HSV negative patients were not significant, 26.4 h vs 13.3 h (all, $p = 0.15$) and 24.2 h vs 12.3 h (negative patients, $p = 0.29$) (Table 1).
- Two patients were prescribed acyclovir but no dose was given because results were reported prior to initiation of treatment.
- Mean time from specimen collection to acyclovir discontinuation for the HSV negative patients was 10.6 hours longer pre-implementation (26.5 h vs 15.9 h; $p < 0.001$), with ranges of 4.2 h - 58.1 h (pre) and 1.4 h - 72.7 h (post) (Figure 4).
- Mean time from specimen collection to acyclovir start and PCR result to acyclovir stop were not significant at 6.9 h vs 5.0 h ($p = 0.2$) and 5.0 h vs 6.7 h ($p = 0.4$), respectively (Figure 4).

Figure 4. Time to Changes in Therapy



CONCLUSIONS

- Implementation of the dHSV PCR assay significantly reduced the average turnaround time from collection to results reporting.
- The more rapid TAT of dHSV impacted patient care and management with the exclusion of HSV infection resulting in a reduction in the duration of potentially unnecessary acyclovir therapy.

ACKNOWLEDGEMENTS

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